THE SYNTHESIS OF PYRAZOLINE DERIVATIVES AND AN EXAMINATION OF THEIR LOCAL ANAESTHETIC ACTIVITY

BY

DAVID RITCHIE, A.R.I.C.

THE SYNTHESIS OF PYRAZOLINE DERIVATIVES AND AN EXAMINATION OF THEIR LOCAL ANAESTHETIC ACTIVITY

INDEX OF PREPARATIONS

New compounds are denoted by an asterisk

* 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate.

* 1-Diethylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4 penten-3-one hydrochloride

* 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate

* 1-Di-n-propylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

* 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate

* 1-Di-n-butylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

* 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate

* 1-Morpholino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-morpholino-ethyl-pyrazoline tartrate

p-n-propoxy-benzylidene-acetone.

* 1-Piperidino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(4'-propoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate

* 1-Dimethylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate.

* 1-Diethylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate.

* 1-Di-n-propylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one-hydrochloride

* 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-di-n-propyl-amino-ethyl-pyrazoline tartrate

* 1-Di-n-butylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-di-n-butyl amino-ethyl-pyrazoline tartrate

p-n-butoxy-benzylidene acetone

* 1-Piperidino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tratrate.

* 1-Dimethylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten 3-one hydrochloride.

* 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate.

* 1-Diethylamino-5-(4'n-butoxyphenyl)-Δ^4-penten-3-one hydrochloride.

* 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate

* 1-Di-n-propylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate

* 1-Di-n-butylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride

* 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate.

The introduction of local anaesthesia into medicine and surgery dates back to 1884 when Koller of Vienna first used cocaine to produce anaesthesia of the cornea. Since that time cocaine has been used extensively for topical and local anaesthesia but its toxic and habit forming properties have led to the search for substitutes which would be free from these disadvantages.

The ideal local anaesthetic should possess the following properties:-

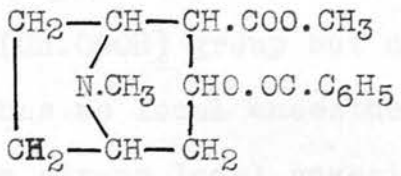
(i) it should produce anaesthesia without causing damage to the nerve tissue;
(ii) it should have low systemic toxicity;
(iii) it should not give rise to the least irritation in the tissues;
(iv) it should be soluble in water, the solution neutral, stable and easily sterilised without decomposition;
(v) it should be compatible with adrenaline and normal saline.

Although many attempts have been made to find such a substance, the perfect local anaesthetic combining all these properties has still to be found.

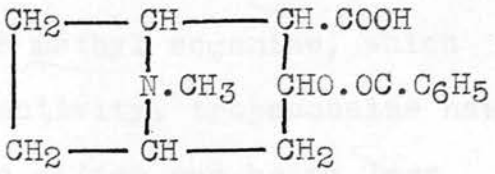
The earliest researches on this problem were directed towards modification of the cocaine molecule (i) in the hope that this would lead to the eliminat-:ion of the undesirable properties. If the methyl group is split off, a compound, benzoyl ecgonine (ii), is produced which has no local anaesthetic activity and although replacement of the methyl group by other alkyl groups, such as ethyl or propyl, gives

compounds /

compounds which are local anaesthetics, these have no advantages over the methyl ester, cocaine, (Merck, Ber., 1885,18,2954).

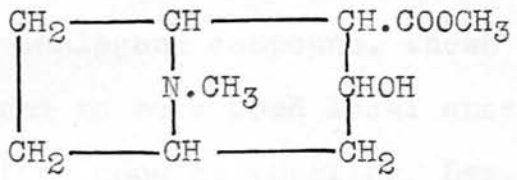


Cocaine (i)



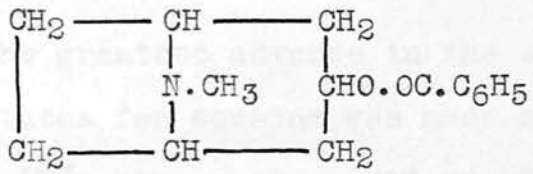
Benzoyl ecgonine (ii)

If the benzoyl group is split off from the cocaine molecule the ecgonine methyl-ester, (iii) has no local anaesthetic activity and replacement of the benzoyl group by other groupings such as isotropyl, valeryl or phenylacetyl gives compounds which have a much lower activity than cocaine itself, (Liebermann, Ber.,1888,21,2347).



Ecgonine methyl-ester (iii)

Closely allied to cocaine is an alkaloid, tropacocaine (iv) which was isolated from Javanese coca and was synthesised by Liebermann (Ber.,1891, 24,2336).

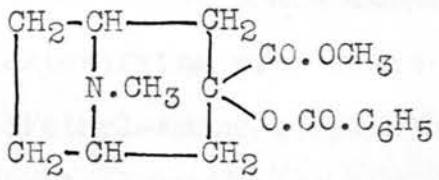


Tropacocaine (iv)

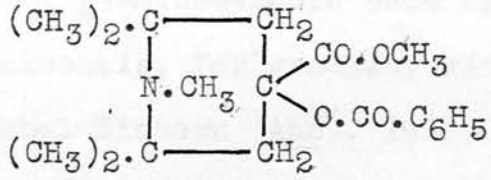
Tropacocaine /

Tropacocaine is benzoyl pseudo-tropeine and has a structure resembling that present in atropine. It differs from methyl ecgonine in having a methylene (CH_2) group in place of the carboxymethylene (CH.COOH) group but unlike methyl ecgonine, which has no local anaesthetic activity, tropacocaine has a strong local anaesthetic action and being less toxic than cocaine was a valuable substitute.

Willstätter (Ber., 1896,29,1575) synthesised α-cocaine (v) which is a further modification of the pseudo tropeine molecule where the methyl ester and the benzoyl group are attached to the same carbon atom. Although very closely allied to cocaine, α-cocaine has no local anaesthetic activity but an analogous compound, known as α-eucaine (vi), was found to be a good local anaesthetic and less toxic than cocaine (Merling, Ber. duet. Pharm. Gesellschaft, 1897,6,173).



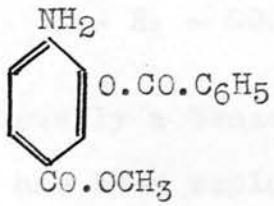
α-Cocaine (v)



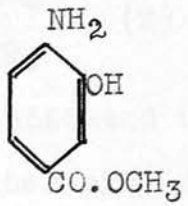
α-Eucaine (vi)

The greatest advance in the synthesis of substitutes for cocaine was made by Einhorn and Heintz (Münchener med., 1897,34,931) when they synthesised a large series of the esters of p-aminobenzoic acid. Einhorn found that the benzoyl derivative of p-amino-m-hydroxy-benzoic-methyl ester (vii) /

(vii) possessed distinct local anaesthetic activity and in contrast to cocaine the removal of the benzoyl group gave a compound (viii) which had greater activity than the benzoyl derivative.



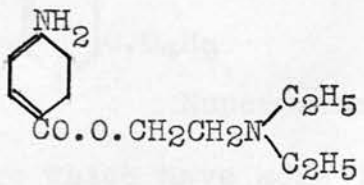
(vii)



(viii)

The amino group of these p-amino-benzoic esters is too weakly basic to form salts and so these compounds are not soluble in water and cannot be used for injection purposes but p-amino-m-hydroxy-benzoyl-methyl-ester (viii) known as Orthoform is used in the form of a dusting powder to anaesthetise exposed nerve endings.

After preparing the simple esters of p-aminobenzoic acid, Einhorn proceeded to synthesise water soluble compounds of p-aminobenzoic acid by esterifying with basic alcohols, for example, with diethyl-amino-ethyl-alcohol Einhorn (Ann., 1910, 371, 125) synthesised procaine (ix) which is an active local anaesthetic about one seventh as toxic as cocaine.



Procaine (ix)

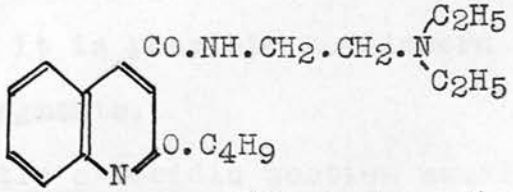
Procaine /

Procaine belongs to the group of compounds which can be represented by the general formulae (x). Many of the more important local anaesthetics in use to-day belong to this group.

$$X - R_1 - CO.O.R_2 - N\begin{matrix}R_3\\R_4\end{matrix} \qquad (x)$$

R_1 is usually a benzene or substituted benzene ring but it has been replaced by other ring structures such as naphthalene, anthracene, pyridine, furan, thiazole, carbazole and quinoline. The substituents of the basic portion, R_3 and R_4 , are usually dimethyl, diethyl, dipropyl, or dibutyl, but the whole basic portion may take the form of a heterocyclic radical such as piperidino, morpholino, pyrrolidino or thiomorpholino.

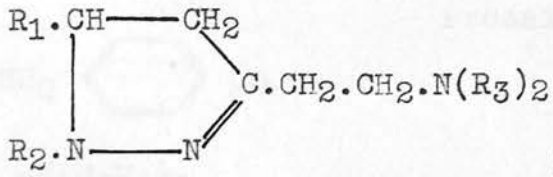
In addition to these esters of p-amino-benzoic acid various other types of compounds have been found to possess local anaesthetic activity. Amongst these is nupercaine (xi) which is an N-alkamine substituted amide of quinoline carboxylic acid and a very potent local anaesthetic. It is ten to twenty times as active as cocaine but is also about five times as toxic.



Nupercaine (xi)

Heterocyclic rings which have more than one hetero atom /

atom in the molecule have also been found to be active local anaesthetics, e.g. pyrazolines of the type (xii) (Nisbet, J.Chem.Soc., 1938,1237).



(xii)

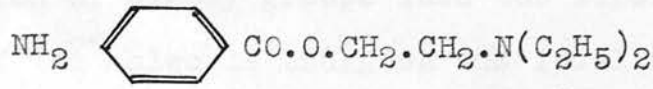
It is true that a study of the structure of compounds which possess local anaesthetic activity reveals no precise relationship between these and their respective activities. As indicated above most of the local anaesthetics in present use are esters and this led Beutner and Calesnick (Anaesthesiology, 1928,12, 141) to make the statement that no compound without an ester grouping could be an efficient and non-irritant local anaesthetic. This is too wide a generalisation as it does not take into account compounds such as nupercaine which is an amide. Indeed it may be mentioned that of the ten local anaesthetics in the British Pharmaceutical Codex 1949, eight are esters, one an alcohol and one an amide.

In the formulae allotted to many local anaesthetics it is possible to discern three important fragments.

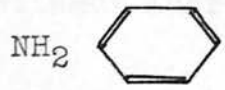
(a) A lipolytic or acidic portion usually containing an aromatic or substituted aromatic structure.
(b) A hydrophilic or basic portion, often containing a tertiary amino group and so capable of salt formation.
(c) An intermediate, usually alkylene chain connecting the lipolytic and hydrophilic portions.

In /

In procaine the fragments (a), (b) and (c) are easily discerned.



Procaine

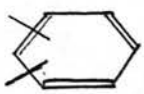
(a) 

(b) $-N(C_2H_5)_2$

(c) $-CH_2-\ CH_2-$

Some effects of varying the substituents in the lipolytic portion of the molecule have been indicated by Büchi et al. (Helv.chim.Acta,1947,30,509) and are shown in Table 1.

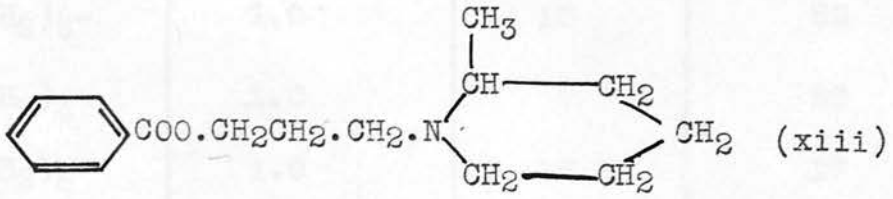
Table 1

Acids from which the lipolytic radical is derived	Substituent	Activity
		+
RHN 	R = Alkyl, Aryalkyl Alkoxy-alkyl Oxyalkyl-oxy Diaklylamino-acyl	+ +
H_2N  R	R = Hydroxyl Alkoxy Amino Halogen	+ + + + +
RO 	R = Hydrogen Alkyl Aryl Dialkylamino-alkyl	(+) + (+)

Further work on the effect of varying the substituents in the lipolytic portion of the local anaesthetic Metycaine (xiii) has been carried out by McElwain and Carney, (J.Amer.Chem.Soc.,1946,68,2592).

The /

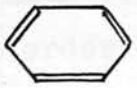
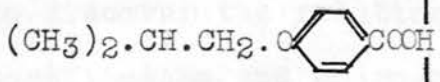
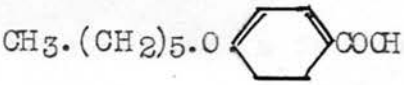
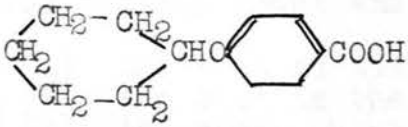
The results as shown in Table 2 indicate that the introduction of alkoxy groups into the lipolytic portion of the molecule enhances the local anaesthetic activity without increasing the toxicity.



(xiii)

Metycaine

Table 2.

Acids from which the lipolytic radical is derived	Concentration per cent	Anaesthesia in mins.	L.D.50;mg./Kg (mice) Intravenous
	1.0	10	22
	0.5	80	32
	0.25	85	23
	0.1	20	54

The alteration of the length of the intermediate chain connecting the lipolytic and hydrophilic portions has an effect upon the local anaesthetic activity of the molecule. The optimum length of the chain varies with different types of compounds. In the Metycaine type, McElwain and Carney (loc.cit.) found that straight chains are more effective than branches chains and for this particular type of molecule the greatest activity was reached when the chain /

chain contained five carbon atoms, see Table 3.

Table 3.

Intermediate chain	Concentration per cent	Anaesthesia min.	L.D.50;mg./kg. (mice) Intravenous
$-(CH_2)_3-$	1.0	10	22
$-(CH_2)_4-$	1.0	7	20
$-(CH_2)_5-$	1.0	17	17
$-(CH_2)_6-$	1.0	15	28
$-CH_2.CH(CH_3)-$	1.0	3	36

The testing of local anaesthetics.

In order to find compounds of clinical value and to discover the relationship between chemical constitution and pharmacological action an accurate method of comparing the activities of local anaesthetics is desirable. The following methods for testing local anaesthetics have been suggested:-

(1) the test in the cornea of the rabbit,
(2) the test in the cornea of the guinea-pig,
(3) the human wheal test,
(4) the guinea-pig wheal test,
(5) the Tuerk test,
(6) the modified Tuerk test,
(7) the digital test on man.

The cornea provides the ideal site for the measurement of surface anaesthetic action for it is free of special sensory cells; the nerve endings are free, unsheathed and embedded in the layer of the cornea. The drug consequently has a single uniform membrane to penetrate after which it is in direct contact /

contact with the sensory nerve fibres. Moreover, the cornea is free of fluid channels and blood vessels. The cornea of the rabbit has normally been used for the carrying out of this test.

The method originally devised by Rider (J.Pharmacol., 1939, 39,329) was to flood the cornea of the rabbit's eye with the drug solution for one minute and then wash out with normal saline in order to keep the duration of exposure constant. The eye was thereafter tested from time to time by applying a stimulus to the cornea and noting the time when there was a return of the reflex response.

The method of Rider was modified by Sinha (ibid., 1936, 57, 199) who extended the time of the application of the drug to five minutes to allow slow acting drugs a better chance to produce their anaesthetic effect. Sinha found considerable variation in the sensitivity of the cornea of different rabbits. A one per cent solution of cocaine hydrochloride applied to the cornea of six rabbits produced full anaesthesia for periods varying from fifteen to twenty-five minutes. The result of Sinha's work showed that there was a concentration of the drug below which no anaesthesia was produced and that there was a short range over which the duration depended upon the concentration. It was also shown that there was an approximate linear relationship between the logarithm of the concentrat-

ion and the duration of anaesthesia.

The cornea of the guinea-pig was found by Chance and Lobstein (ibid., 1944,82,203) to give more consistent results than the cornea of the rabbit. It was found that there was a more regular response to stimuli and that there was no significant difference between the response of the right and the left eye to the application of the drug. In this case the drug was dissolved in normal saline and applied to the cornea by means of a dropping tube. The first stimulus was applied to the eye after the lapse of forty-five seconds and repeated each minute for five minutes. The stimulus used was a horse hair attached to a glass rod and applied in such a manner that there was the same degree of curvature at each application. The number and percentage of the stimuli failing to exhibit a blink response were recorded for each animal and each dose. It was found that there was a linear relationship between the probit percentage response and the logarithm of the concentration.

The "Human Wheal" method was also used by Sinha (loc.cit.) for the estimation of the duration of anaesthesia. The drug was dissolved in normal saline and injected intradermally into the human arm and a stimulus applied at regular intervals. The stimulus used was the prick of a pin. Here it was found again that there was an approximate linear relationship /

relationship between the logarithm of the concentration and the duration of the anaesthesia. This was a most valuable observation as it made it possible to compare, with some degree of accuracy, the activity of one local anaesthetic with another as standard.

The shaved back of the guinea-pig was used by Bülbring and Wajda (ibid., 1945,85,78) instead of the human wheal. It was found that the guinea-pig gave a prompt and reliable response to the prick of a pin on the shaved surface of its back. The drug to be tested was dissolved in normal saline and injected intradermally into the shaved back and the wheal produced outlined in ink. The marked area was tested every five minutes for thirty minutes by pricking six times with a pin and the number of times the pricks failed to elicit a response recorded. The negative responses were added up and out of a possible thirty-six gave an indication of the degree of anaesthesia. Since the front and rear areas of the back of the guinea-pig were not equally responsive, duplicate injections of each concentration were made at the front and rear and mean responses recorded. It was found that there was an approximate linear relationship between the anaesthetic effect, measured in the arbitary units described, and the logarithm of the various concentrations used, and that for different drugs, apart from cocaine, the lines were approximately parallel, Fig. No. 1.

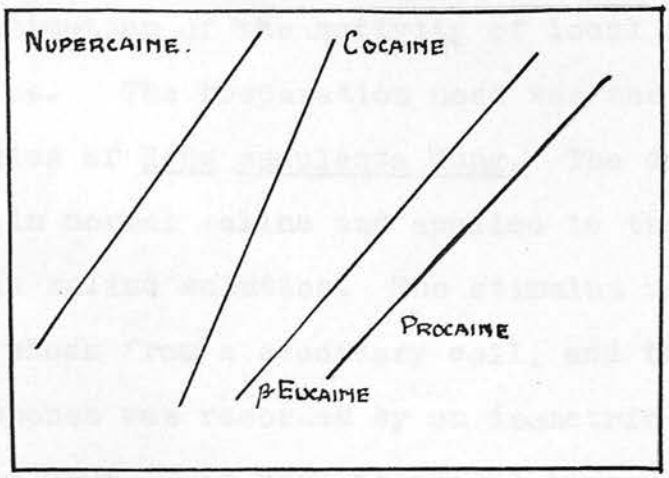


Figure No. 1.

It was suggested that the difference in the slope of the regression line for cocaine was due to its vasoconstrictor effect and this was confirmed when it was shown that by the addition of adrenaline to procaine the regression line was brought parallel to that for cocaine, Fig. No. 2. For comparison of the respective activities of local anaesthetics it was therefore suggested that for this particular test procaine would be a better reference standard than cocaine.

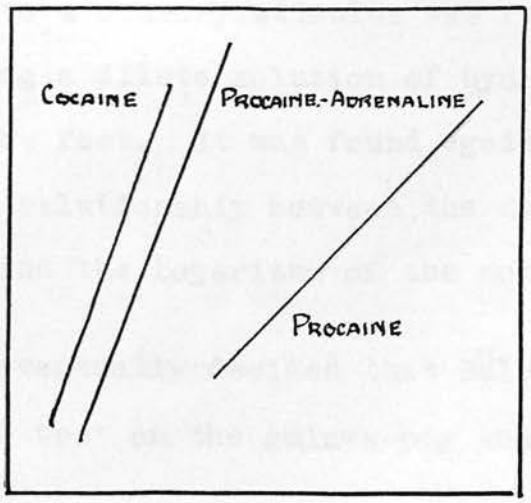


Figure No. 2.

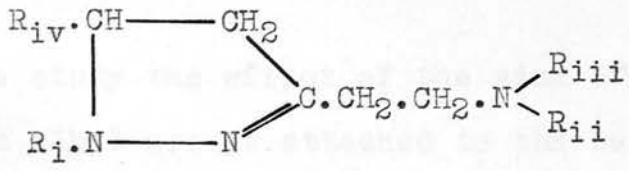
A method depending upon the paralysis of the frog's sciatic nerve was used by Sinha (loc.cit.) for the estimation of the activity of local anaesthetics. The preparation used was the sciatic-gastrocnemius of Rana esculenta Hung. The drug was dissolved in normal saline and applied to the muscle immersed in saline solution. The stimulus used was the break shock from a secondary coil, and the muscle response was recorded by an isometric lever on a smoked drum. The results showed that reliable results could only be obtained if averages were made from a large number of experiments.

A method depending upon plexus anaesthesia in frogs was developed by Bülbring and Wajda (loc.cit) The frog, Rana temporaria, was decapitated and the upper part of the spinal cord destroyed down to the level of the third vertabrae. The viscera was removed by a transverse incision in the abdominal wall and the local anaesthetic, dissolved in normal saline, run into the pocket formed by the lower abdomen. The time taken to abolish the reflex contraction to a sensory stimulus was recorded, the stimulus being a dilute solution of hydrochloric acid applied to the feet. It was found again that there was a linear relationship between the duration of anaesthesia and the logarithm of the concentration.

It was eventually decided that Bülbring and Wajda's wheal test on the guinea-pig and the test on the

the guinea pig cornea devised by Chance and Lobstein were to be the methods employed in this investigation, although a number of experiments were made on the rabbit's cornea.

It had already been shown by H.B.Nisbet *et al.* (J.Chem.Soc., 1938, 1568) that pyrazolines of the type "A_1".



"A_1"

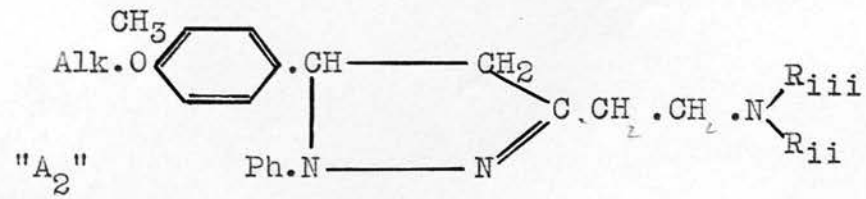
possessed local anaesthetic activity and that when R_{iv} is a phenyl nucleus with alkoxy substituents that an increase in activity and a decrease in toxicity occurred, Table 4.

Table 4.

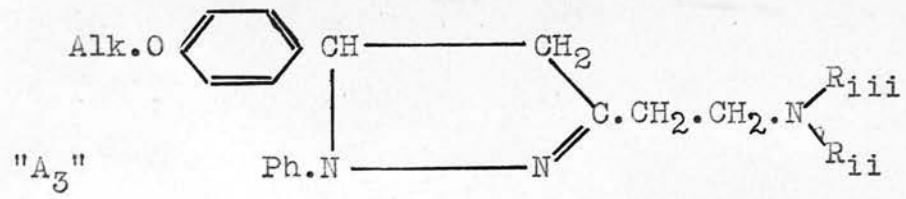
Compound	Relative effective activity to cocaine	Relative toxicity to cocaine
Cocaine hydrochloride	1	1
R_{iv} = phenyl	5	2.2
R_{iv} = 3'-ethoxy-4'-methoxyphenyl	10	1.5
R_{iv} = 2'-*n*-butoxyphenyl	50	0.6

It had also been shown by Nisbet and Levvy (J.Pharmacol., 1939, 65, 129) that a further increase in activity and decrease in toxicity occurred when a *n*-butoxy substituent was in the 2'-position on the R_{iv} phenyl nucleus, Table. 4.

The present investigation was planned to study the effect of the alkoxy groups in the compounds of the type "A_2" and "A_3".



"A_2"



and also to study the effect of the size of the substituent alkyl groups attached to the basic nitrogen atom in the 3-amino-ethyl group.

CHEMICAL DISCUSSION

The pyrazoline compounds which it was proposed should be prepared for an examination of their anaesthetic properties were synthesised by the following steps:-

(1) A substituted β-amino-ethyl unsaturated ketone of the type (xvii) was synthesised from an unsaturated methyl ketone (xiv), formaldehyde and a sec.-base hydrochloride (xvi) by the application of the Mannich reaction:-

$$\underset{(xiv)}{R.CH=CH.CO.CH_3} + \underset{(xv)}{CH_2O} + \underset{(xvi)}{HNR_2,HCl} \xrightarrow{-H_2O} \underset{(xvii)}{R.CH=CH.CO.CH_2.CH_2.NR_2,HCl}$$

(2) The compounds of the type (xvii) were converted to their phenylhydrazones (xviii) and these isomerised to the pyrazolines (xix):-

$$R.CH=CH.CO.CH_2.CH_2.NR_2,HCl \quad (xvii) + Ph.NH.NH_2 \xrightarrow{-H_2O}$$

$$\underset{(xviii)}{R.CH=CH.C(=N.NH.Ph).CH_2.CH_2.NR_2,HCl} \longrightarrow \underset{(xix)}{R.CH(-Ph.N)-CH_2-C(=N-)-CH_2.CH_2.NR_2,HCl}$$

The Mannich Reaction.

The reaction used in step (1) is a general one which involves the condensation of ammonia or a primary or a secondary amine with formaldehyde and a compound containing at least one hydrogen of pronounced activity. The essential part of the reaction is the replacement of the active hydrogen atom by an aminoethyl group or substituted aminoethyl group. An example of such a reaction is the condensation of acetophenone, formaldehyde, and dimethylamine hydrochloride, to give 1-dimethylamino-3-phenyl-3-one hydrochloride:-

$$C_6H_5.CO.CH_3. + CH_2O + H.N.(CH_3)_2,HCl \longrightarrow C_6H_5.CO.CH_2.CH_2.N.(CH_3)_2,HCl + H_2O$$

The product from a methyl-ketone still contains an active hydrogen atom and in some cases it is possible to form a compound with two basic groups:-

$$C_6H_5.CO.CH_2.CH_2.N.(CH_3)_2,HCl + CH_2O + H.N.(CH_3)_2,HCl \longrightarrow C_6H_5.CO.CH\ CH_2.N(CH_3)_2,HCl_{\ 2} + H_2O$$

The first observation on the reaction was made by Schafer and Tollens (Ber., 1903, 36, 1358), who isolated the tertiary amine from the condensation of ammonium chloride, formaldehyde, and acetophenone. Further studies were made on the reaction by Petrenko-Kritschenko (Ber., 1906, 39, 1351). The detailed study of the reaction was started by Mannich (Arch.Pharm., 1917, 255, 261) who has since extensively explored the reaction and its possible uses in synthesis.

The/

The mechanism of the reaction has not been established. It has been suggested that the addition of the amine to the formaldehyde is an intermediate step in the reaction (Bruson and Butler, J.Am.Chem.Soc., 1946, 68, 2348):-

$$R_2.NH + CH_2O \longrightarrow R_2N.CH_2.OH$$

But the fact that with antipyrine the reaction of dimethylaminomethanol gives a poorer yield of the condensation product than with formaldehyde and the amine hydrochloride ~~does~~ suggests that this theory of the course of the reaction is not correct.

Another suggestion offered is that the first step in the reaction is the formation of the methylol from the ketone and the formaldehyde:-

$$R.CO.CH_3 + CH_2O \longrightarrow R.CO.CH_2.CH_2.OH$$

The methylols of acetone and cyclohexanone have been found to condense with dimethylamine to give good yields of the expected products and would appear to confirm this theory of the reaction. On the other hand however antipyrine does not react with dimethylamine (Bodendorf and Koralewski, Arch.Pharm., 1933, 271, 101). It would appear therefore that neither of these suggestions represents the mechanism of the Mannich reaction.

Since Mannich first demonstrated this reaction as a general method of synthesis, many types of compounds/

compounds have been found to react in this way. Some examples are given below.

Mannich Reaction with Ketones.

Ketones have been found particularly useful in this type of reaction and many condensations of such compounds with primary and secondary amines have been carried out.

Aliphatic Ketones.

Ketones such as acetone, methylethyl ketone, methylpropyl ketone have been condensed with ammonia and various primary and secondary amines, e.g. (1) acetone with methylamine and (2) with dimethylamine:-

(1) $CH_3.CO.CH_3. + CH_2O + H_2N.CH_3,HCl \longrightarrow (CH_3.CO.CH_2.CH_2.)_2N.CH_3,HCl + H_2O$

(2) $CH_3.CO.CH_3. + CH_2O + HN.(CH_3.)_2,HCl \longrightarrow CH_3.CO.CH_2CH_2.N.(CH_3)_2,HCl$

(Mannich, Arch.Pharm., 1917, 255, 261).

When diethyl-ketone was condensed with formaldehyde and methylamine hydrochloride a mixture was obtained which contained among other products a bis derivative and a breakdown product of the primary condensation product (Mannich, loc.cit.):-

$C_2H_5.CO.CH_2.CH_3 + CH_2O + H_2N.CH_3.HCl \longrightarrow C_2H_5.CO.CH(CH_3).CH_2.NH.CH_3,HCl + H_2O$

$+C_2H_5.CO.C_2H_5 \quad CH_2O \qquad C_2H_5CO.C(CH_3):CH_2 + H_2N.CH_3$

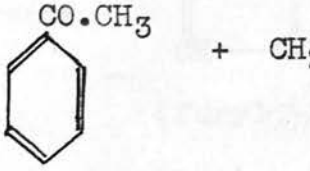
$C_2H_5.CO.CH(CH_3).CH_2 \diagdown$

$N.CH_3,HCl$

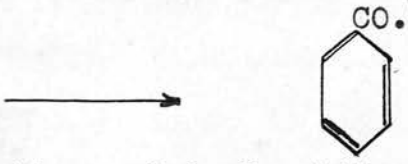
$C_2H_5.CO.CH(CH_3).CH_2 \diagup$

Mannich reaction with aliphatic aromatic ketones.

Acetophenone and dimethylamine hydrochloride condense with formaldehyde to form 1-dimethylamino-3-phenyl-penten-3-one hydrochloride (Mannich and Neilner, Ber., 1922, 55, 356):-

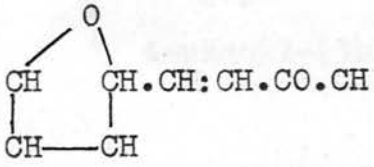


+ CH_2O + $HN(CH_3)_2$,HCl



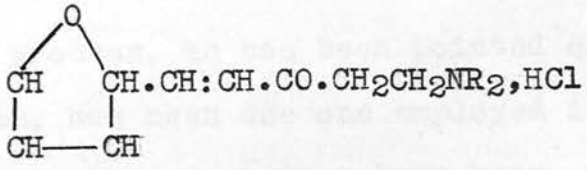
+H_2O

β-Amino derivatives of furfurylidene acetone were prepared by H.B. Nisbet and C.G. Gray (J.Chem.Soc., 1930, 52, 235) from the condensation of furfurylidene-acetone, formaldehyde and secondary amine hydrochlorides:-



+ CH_2O + $HN.R_2$,HCl

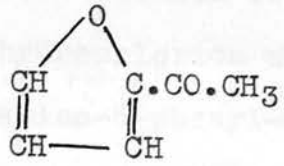
Furfurylidene acetone



+ H_2O

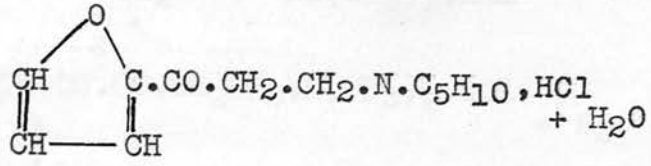
1-dialkylamino-5-(furyl-2)-Δ^4-penten-3-one hydrochloride

The preparation of furyl-2-β-piperidinoethyl-ketone and 4-phenyl-(thiazyl-2)-β-piperidinoethyl-ketone were carried by Levvy and Nisbet (J.Chem.Soc., 1938, 1053) utilising the Mannich reaction.

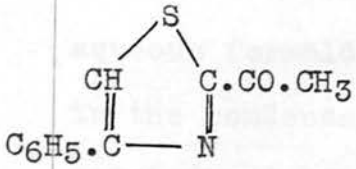


+ CH_2O + $HN.C_5H_{10},HCl$

2-acetylfuran

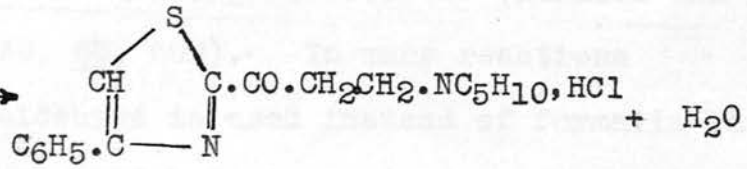


(furyl-2)-β-piperidinoethyl ketone hydrochloride



+ CH_2O + $HN(C_5H_{10}).HCl$

4-phenyl-2-acetylthiazole

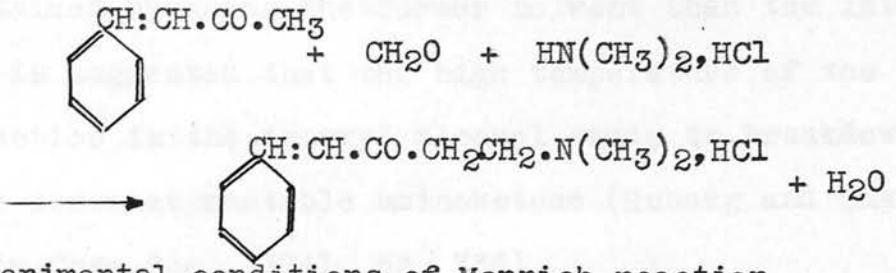


4-phenyl-(thiazyl-2)-β-piperidinoethyl ketone hydrochloride

The Mannich reaction has been used in condensation reactions with various unsaturated ketones, and this process, as has been pointed out in the introduction, has been the one employed in this investigation. Various amines have been condensed with benzalacetone, 4-anisalacetone, piperonalacetone, 3-methoxy-4-ethoxybenzalacetone, 3-ethoxy-4-methoxy-benzalacetone. (H.B. Nisbet, J.Chem.Soc., 1938, 1237; 1938, 1568).

One example of such a reaction is the condensation/

condensation of benzalacetone and dimethylamine hydrochloride with formaldehyde to give 1-dimethylamino-5-phenyl-Δ^4-penten-3-one hydrochloride:-



Experimental conditions of Mannich reaction.

In the original work carried out by Mannich, aqueous formaldehyde in 20 to 40% solution was used in the condensation. In this case the reaction is carried out by shaking or stirring the reactants in the absence of an organic solvent (Mannich and Mohs, Ber., 1930, 63, 608). In many reactions paraformaldehyde is used instead of formalin but when paraformaldehyde is used an organic solvent is necessary. Ethyl alcohol (95 - 100%) is generally used when the reactant is a ketone. In some condensations the reaction proceeds faster in higher boiling solvents. Thus in the condensation of 2-acetylphenanthrene with paraformaldehyde and secondary amines, isoamyl alcohol has been found to be a more suitable solvent. With the higher boiling solvent the reaction proceeds more smoothly and generally higher yields are obtained, but this is not a general condition for in some reactions the higher temperature leads to lower yields. When 3-acetyl-9-methylcarbazole is condensed with formaldehyde/

formaldehyde and a secondary amine salt it is found that although the reaction proceeds more slowly in ethyl than in isoamyl alcohol, better yields are obtained by using the former solvent than the latter. It is suggested that the high temperature of the reaction in the isoamyl alcohol tends to breakdown the somewhat unstable aminoketone (Ruberg and Small, J.Am.Chem.Soc., 1941, 63, 736).

The time of reaction varies according to the components used. Some reactions are completed in a few minutes, while others even after several hours refluxing do not proceed to completion. The reaction between furfurylidene acetone, paraformaldehyde and dimethylamine hydrochloride is said to be complete in a few minutes (Nisbet and Gray, loc.cit), while on the other hand when 3-acetyl-9-methylcarbazole is condensed with paraformaldehyde and diethylamine hydrochloride in absolute alcohol, the yield after heating five hours is 59% and after heating eight hours is 83% (Ruberg and Small, loc.cit.).

The relative amounts of the different components also varies with different reactions. The usual custom is to use 1.0 mol. equivalent of the carbonyl compound, 1.05 - 1.10 mol. equivalents of the amine salt and 1.5 - 2.0 mol. equivalents of formaldehyde or paraformaldehyde. Excess of paraformaldehyde appears to be necessary to bring about the completion/

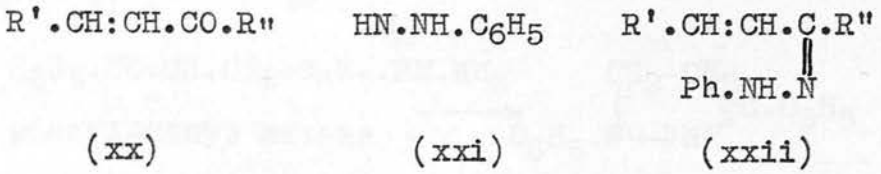
completion of the reaction especially if ethyl alcohol is used as the solvent for in this case part of the formaldehyde reacts with the ethyl alcohol to form a methylene-diethyl ether (Mannich and Schütz, Arch.Pharm., 1927, 265, 684). The formaldehyde or paraformaldehyde is not all added at one time but in several portions during the course of the reaction. The various amounts of the components also depend on how easily the final product is isolated and if more than one product is possible the proportion of the various components will influence the nature of the final product.

In many cases the reaction product crystallises on cooling. If this does not occur the addition of anhydrous ether sometimes assists the separation; alternatively, removal of the original solvent and recrystallisation of the product from ether or acetone is recommended. It is also possible in some cases to isolate the base from its salt and purify by distillation but this may be accompanied by decomposition as many of the products are unstable.

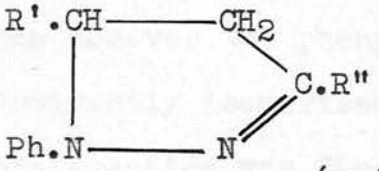
(2) Synthesis of 1:3:5-trisubstituted pyrazolines.

The general reaction for the preparation of pyrazolines from α -unsaturated ketones (xx) is accomplished by treating with phenylhydrazine (xxi) to form the phenylhydrazones (xxii) and

subsequent cyclization of the phenylhydrazone (xxii) to the pyrazoline (xxiii) thus:-

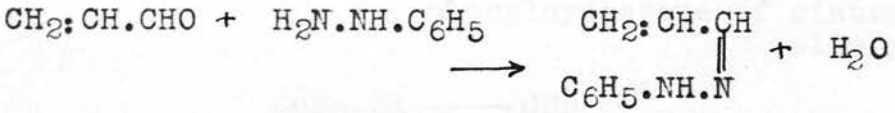


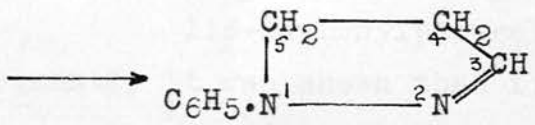
(xx) (xxi) (xxii)



(xxiii)

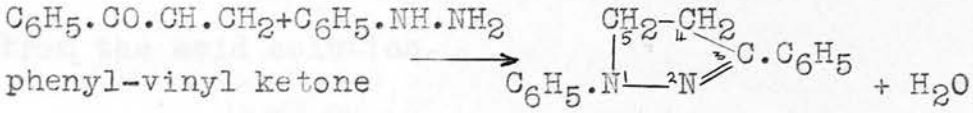
In some cases it is not possible to isolate the intermediate phenylhydrazone. Thus, when acrolein was treated with phenylhydrazine the only product isolated was 1-phenylpyrazoline (E.Fischer and O.Knoevenagel, Ann., 1887, 239, 294):-





1-phenyl-pyrazoline

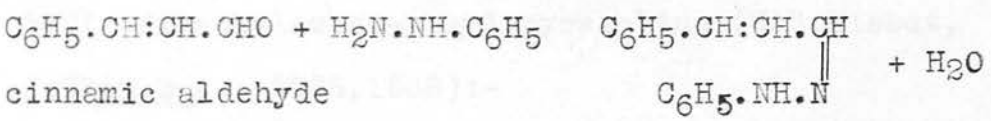
Similarly Kohler (J.Am.Chem.Soc., 1909,42,375) found that phenyl-vinyl ketone and phenylhydrazine reacted to form 1:3-diphenylpyrazoline:-



phenyl-vinyl ketone

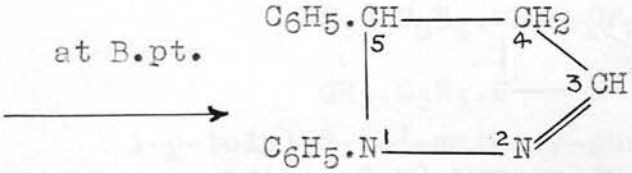
1:3-diphenylpyrazoline

In most cases however the phenylhydrazone is isolated and subsequently isomerised to the pyrazoline. This reaction was first carried out by the distillation of the phenylhydrazone, e.g. 1:5-diphenylpyrazoline was formed by the distillation of the phenylhydrazone of cinnamic aldehyde (Laubmann, Ber., 1888,21,1213):-



cinnamic aldehyde

phenylhydrazone of cinnamic aldehyde

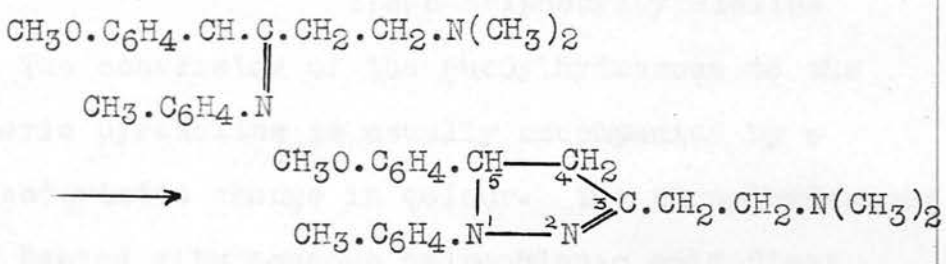


1:5-diphenylpyrazoline

Subsequently it was shown that 1:5-diphenylpyrazoline and other pyrazolines could be obtained by heating the phenylhydrazones with acetic acid (K.Auwers and K. Muller, Ber., 1908, 41, 4232). Later H.B. Nisbet and C.G. Gray /

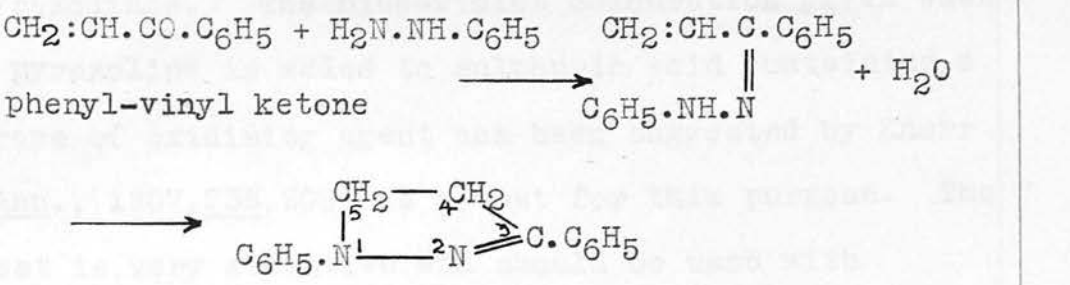
C.G. Gray (J.Chem.Soc., loc.cit.) found that this reaction could be more conveniently carried out by heating with aqueous hydrochloric acid. By the latter method the hydrochlorides of the pyrazolines were formed and in many cases crystallised readily from the acid solution.

Substituents groups in the 1-position of the pyrazoline nucleus are formed when substituted hydrazines are used to form the hydrazones. Thus phenylhydrazine gives a phenyl radical attached to the nitrogen in the 1-position. Another substituted hydrazine which has been used is p-tolylhydrazine, e.g. the p-tolylhydrazone of 1-dimethylamino-5-(4'-methoxy-phenyl)-Δ^4-penten-3-one on heating with acetic acid gives 1-p-tolyl-5-(4'-methoxy-phenyl)-3-β -dimethylamino-ethyl pyrazoline (H.B.Nisbet, J.Chem.Soc., 1938,1568):-



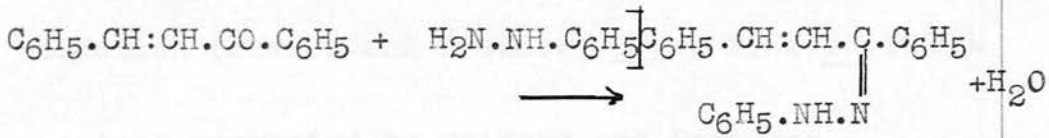
1-p-tolyl-5-(4'-methoxy-phenyl)-3-β-dimethyl amino ethyl pyrazoline.

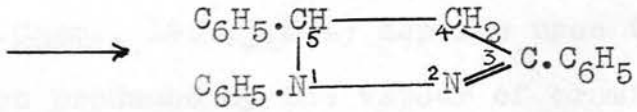
If the substituted hydrazone is derived from a ketone then the pyrazoline has a substituent group attached to the carbon atom in the 3-position, e.g. phenyl-vinyl ketone gives a phenyl radical attached to the 3-position of the pyrazoline nucleus:-



1:3-diphenylpyrazoline

Substitution in the 5-position of the pyrazoline molecule takes place when the vinyl group of the ketone forming the hydrazone carries a substituent radical. Thus benzalacetophenone gives rise to a phenyl radical substituted in the 5-position of the pyrazoline nucleus :-





1:3:5-triphenylpyrazoline

The conversion of the phenylhydrazone to the isomeric pyrazoline is usually accompanied by a characteristic change in colour. The phenylhydrazone when heated with aqueous hydrochloric acid first turns a brick-red and finally a green coloured solution is formed. Many of the pyrazolines fluoresce in solution and this fluorescence is made more evident when the solution is viewed under an ultra-violet lamp.

Several tests have been suggested to distinguish between the phenylhydrazones and their isomeric pyrazolines. /

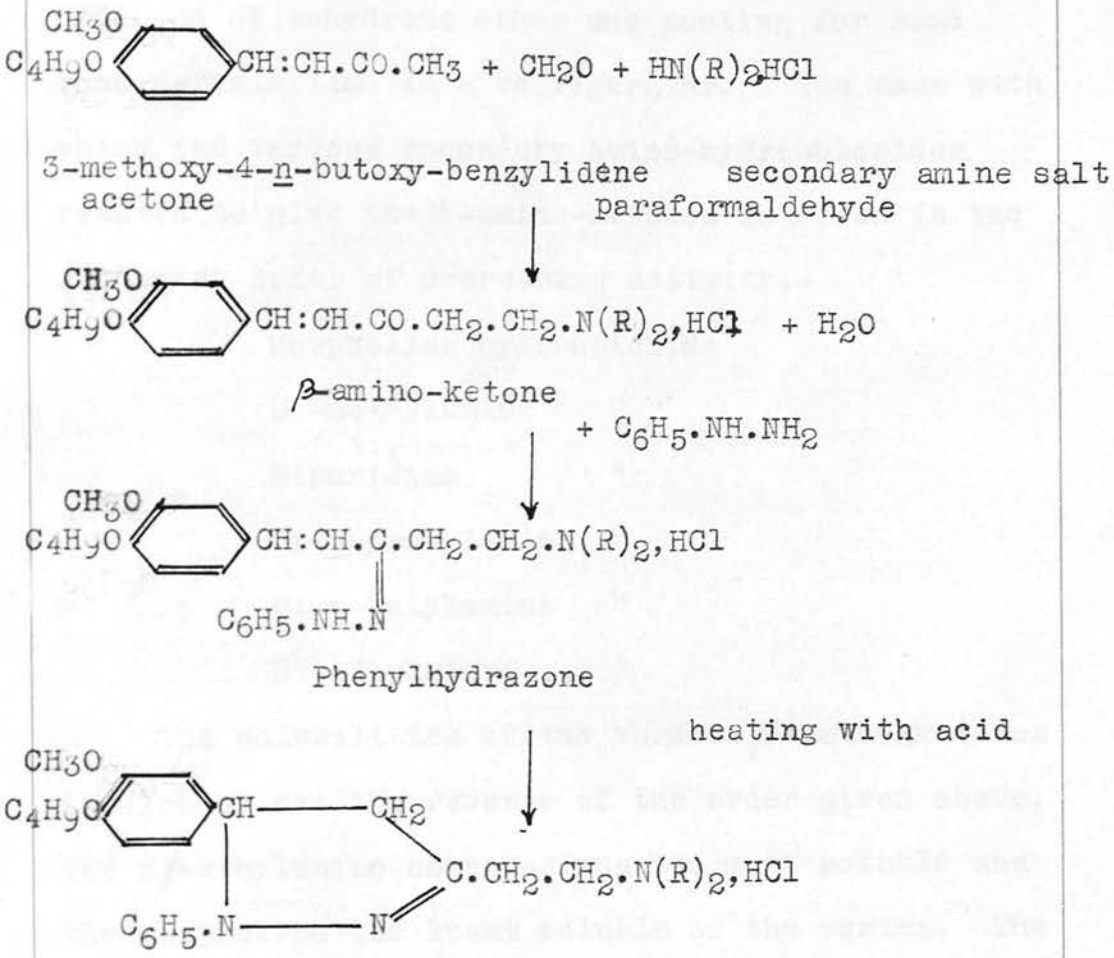
pyrazolines. The blue-violet colouration given when a pyrazoline is added to sulphuric acid containing a trace of oxidising agent has been suggested by Knorr (Ann., 1887,238,200) as a test for this purpose. The test is very sensitive and should be used with caution as a trace of pyrazoline in the phenylhydrazone is sufficient to give a positive reaction.

Tafel (Ber.,1889,22,1854) describes a test depending upon the production of aniline from the phenylhydrazone by reduction with sodium amalgam in acid, but this test has been found unreliable as many of the phenylhydrazones did not give aniline on reduction (Auwers and Kreuder, Ber., 1925,58,1926).

A test suggested by Raiford and Paterson (J.Org.Chem., 1937,1,544) depends upon the colour reaction produced by the vapour of bromine. On exposure to bromine vapour the phenylhydrazone turns a red-orange and the pyrazoline a green colour. This test when applied to the pyrazolines of the present series gave a positive reaction. The pyrazolines gave an immediate green colour when exposed to the vapour of bromine.

1) Derivatives of 3-methoxy-4-n-butoxy benzylidene-acetone

The first series of compounds synthesised in the present study were β-amino-ketones and related pyrazolines derived from 3-methoxy-4-n-butoxy-benzylidene acetone, e.g.:-



Where R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, NC_5H_{10}, $N(CH_2)_4O$.

Preparation of the β-amino-ketones

The separation of the β-amino-ketones from the reactant solution varied according to the secondary amine being used. It was found that the morpholino, di-methylamino and piperidino compounds crystallised readily from the solution but that the di-n-propyl-amino and the di-n-butylamino compounds were much slower and required extra cooling. The di-ethylamino compound /

compound was only isolated with difficulty. Prolonged heating of the reactants and variation of their respective quantities had no beneficial effect. It was finally isolated, in low yield, by the addition of anhydrous ether and cooling for some considerable time in a refrigerator. The ease with which the various secondary amine-hydrochlorides reacted to give the β-amino-ketones is given in the following order of decreasing activity:-

Morpholine hydrochloride
Di-methylamine "
Piperidine "
Di-n-propylamine "
Di-n-butylamine "
Di-ethylamine "

The solubilities of the various β-amino-ketones in alcohol was the reverse of the order given above. The di-ethylamino compound was the most soluble and the morpholino the least soluble of the series. The β-amino-ketones were readily re-crystallised from alcohol or alcohol-ether.

Preparation of the phenylhydrazones.

The phenylhydrazones were prepared by the addition of phenylhydrazine to an alcoholic solution of the β-amino-ketone in the presence of acetic acid. The phenylhydrazones of the morpholino, di-methyl-amino and piperidino compounds crystallised rapidly from solution while those of the di-ethylamino, di-n-propylamino and di-n-butylamino were slower and required /

required seeding. The ease of formation of the phenylhydrazones is given in the following order of decreasing activity:-

Morpholino compound
Di-methylamino "
Piperidino "
Di-ethylamino "
Di-n-propylamino "
Di-n-butylamino "

The solubilities of the phenylhydrazones in alcohol were in the reverse of the above order, the morpholino compound being the least soluble and the di-n-butylamino the most soluble.

Preparation of the pyrazolines.

The pyrazolines were formed from the phenylhydrazones by heating with N/1 hydrochloric acid. The hydrochlorides of the piperidino and di-methylamino compounds were isolated as crystalline solids but the other members of the series formed viscous oils which resisted crystallisation. The tartrates of the bases were formed without difficulty.

The hydrochlorides were only slightly soluble in water (0.1 - 0.3%) but the tartrates were more soluble (1.0 - 2.0%).

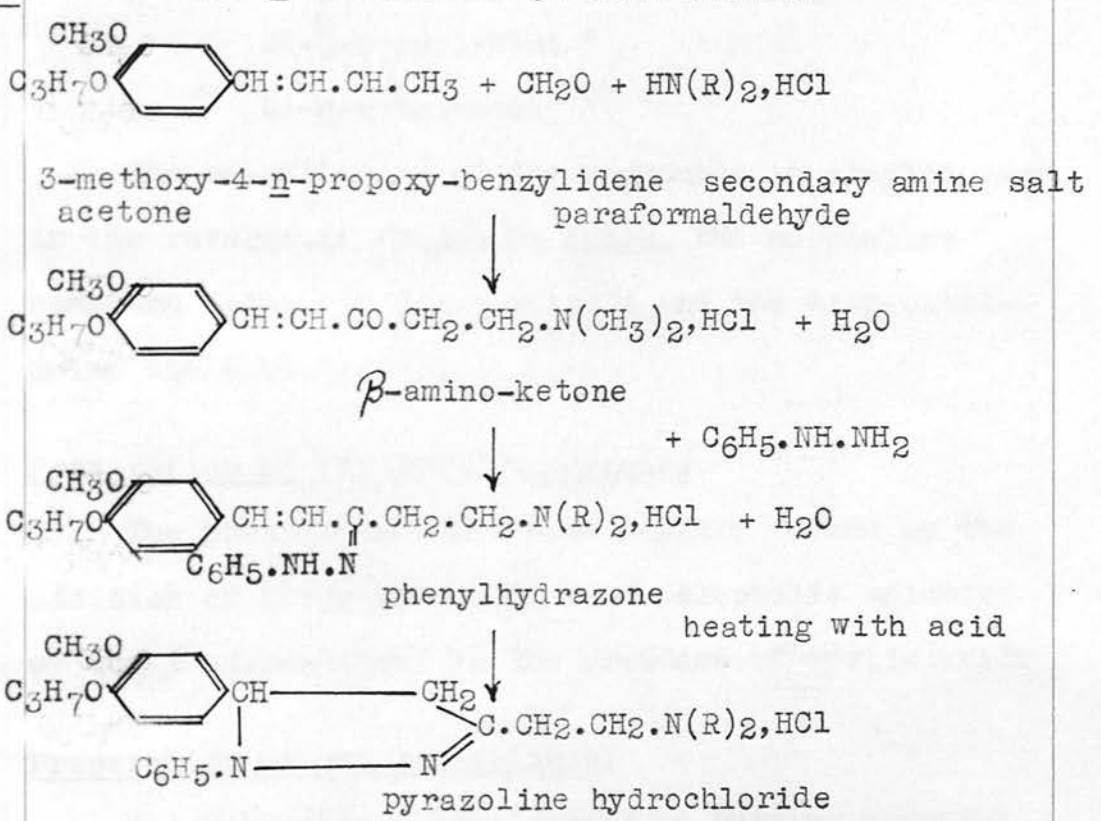
Knorr's test was given by all the pyrazolines and exposure of a small amount to the vapour of bromine gave an immediate green colouration.

All /

All the pyrazoline tartrates gave a local anaesthetic action when a small portion was placed on the tip of the tongue. Although this is only a rough test, it was possible to detect the difference between the diethylamino compound which gave a strong action and the morpholino compound which gave a weak action.

2) Derivatives of 3-methoxy-4-n-butoxy benzylidene-acetone

Similarly were prepared a series of β-amino-ketones and related pyrazolines derived from 3-methoxy-4-n-propoxy-benzylidene-acetone.



Where R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, NC_5H_{10}, $N(CH_2)_4O$.

Preparation of the β-amino-ketones

The β-amino-ketones were prepared by the Mannich reaction as in the previous series and a somewhat similar variation in the ease of the separation of the β-amino-ketones occurred. The morpholino, di-methylamino /

di-methylamino and piperidino compounds crystallised readily but again the di-ethylamino compound was slow in crystallising but with less difficulty and in better yield than in the previous series. The ease of formation of the β-amino-ketones is given in the following order of decreasing activity:-

Morpholino compound
Di-methylamino "
Piperidino "
Di-ethylamino "
Di-n-propylamino "
Di-n-butylamino "

The solubilities of the compounds in alcohol were in the reverse of the above order, the morpholine compound being the least soluble and the di-n-butyl-amino the most soluble.

Preparation of the phenylhydrazones.

The phenylhydrazones were readily formed by the addition of phenylhydrazine to an alcoholic solution of the β-amino-ketone in the presence of acetic acid.

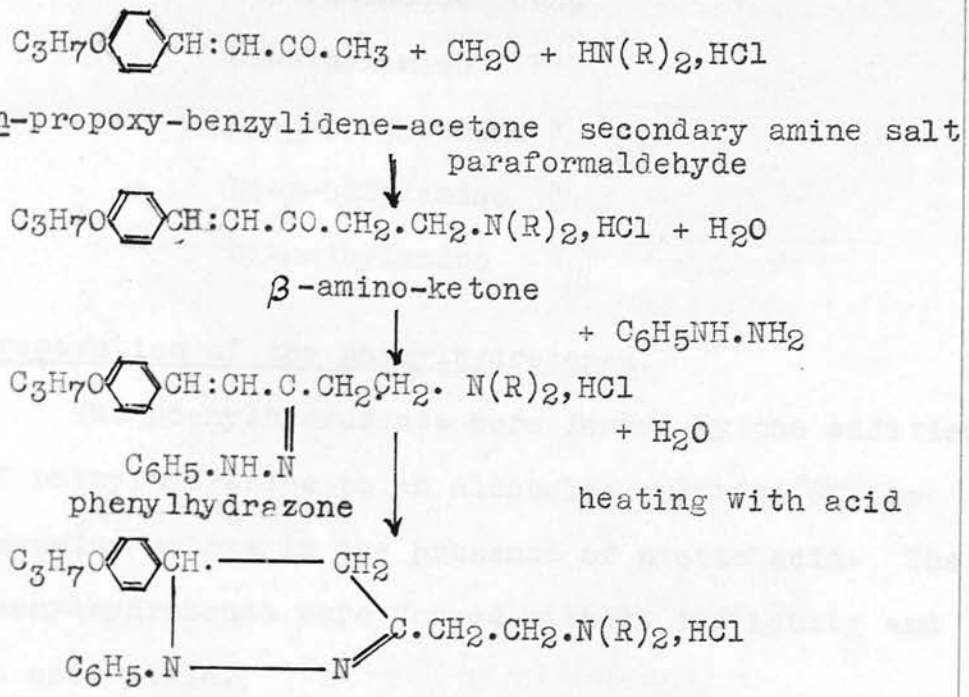
Preparation of the pyrazolines.

The pyrazolines were formed by heating with N/1 hydrochloric acid. When the phenylhydrazone of the morpholine compound was heated with acid the conversion to the isomeric pyrazoline did not take place but on the addition of twenty per cent. of ethyl alcohol the conversion took place smoothly.

In a similar manner were prepared a series of β-amino-ketones /

) Derivatives of 4-n-propoxy-benzylidene-acetone

ketones and related pyrazolines from 4-n-propoxy-benzylidene-acetone.



Pyrazoline hydrochloride

Where R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, NC_5H_{10}.

Preparation of β-amino-ketones.

The β-amino-ketones were prepared by the Mannich reaction as in the previous series. In this group contrary to the experience of the two previous series, the di-ethylamino compound crystallised readily from the reactant solution but more difficulty was experienced in the formation of the di-methylamino compound. In the latter case the experiment was repeated and the time of heating and the relative quantities of the reactants varied but no improvement in the reaction was noted. The compound was finally isolated by adding an excess of anhydrous ether and cooling at a low temperature. The ease of formation of the β-amino-ketone is given in the following order of decreasing /

decreasing activity:-

Piperidino compound

Di-ethylamino "

Di-n-propylamino "

Di-n-butylamino "

Di-methylamino "

Preparation of the phenylhydrazones.

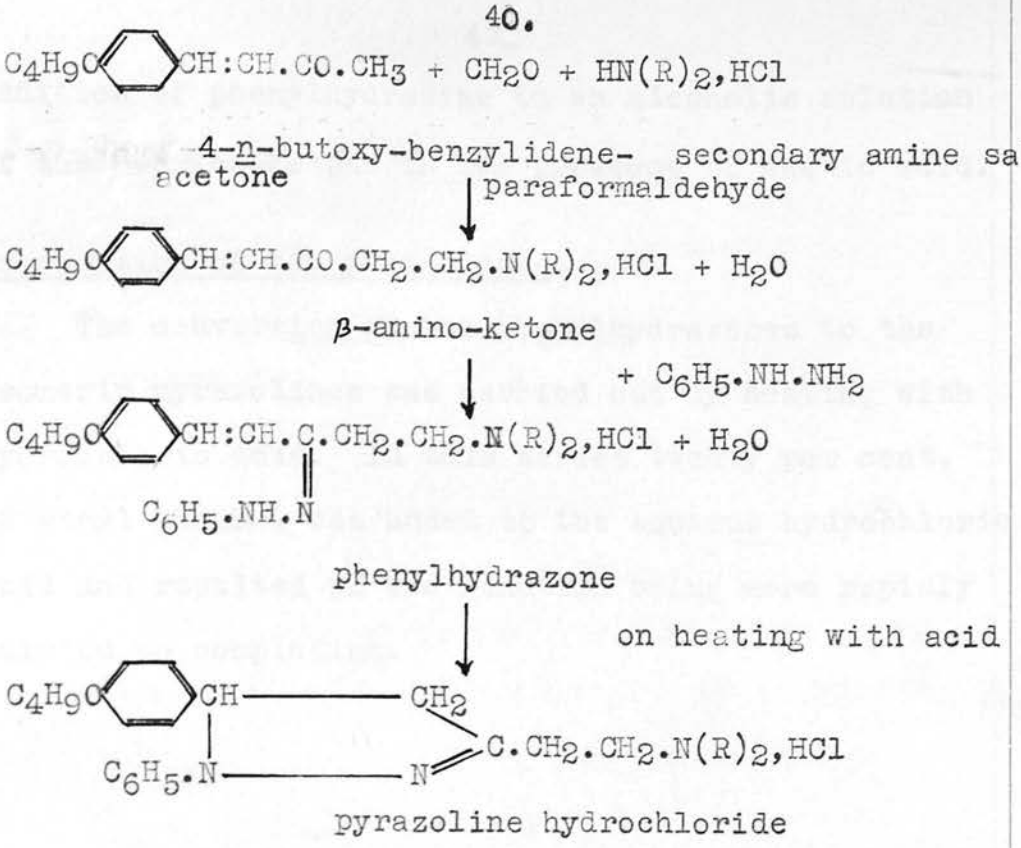
The phenylhydrazones were formed by the addition of phenylhydrazine to an alcoholic solution of the β-amino-ketone in the presence of acetic acid. The phenylhydrazones were formed without difficulty and in good yield.

Preparation of the pyrazolines.

The conversion of the phenylhydrazones to the isomeric pyrazolines was carried out by heating with aqueous hydrochloric acid.

f) Derivatives of 4-n-butoxy-benzylidene acetone

Similarly were prepared a series of β-amino-ketones and related pyrazolines derived from 4-n-butoxy-benzylidene-acetone, see over.



pyrazoline hydrochloride

Where R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, NC_5H_{10}.

Preparation of the β-amino-ketones.

The β-amino-ketones were prepared by the Mannich reaction as in the previous series. The reactions were carried out without difficulty and good yields of the products were obtained.

The solubility of the compounds in alcohol were in the following order of decreasing solubility:-

Dimethylamino compound
Piperidino "
Di-ethylamino "
Di-n-propylamino "
Di-n-butylamino "

Preparation of the phenylhydrazones.

The phenylhydrazones were readily formed by the addition /

addition of phenylhydrazine to an alcoholic solution of the β-amino-ketone in the presence of acetic acid.

Preparation of the pyrazolines.

The conversion of the phenylhydrazones to the isomeric pyrazolines was carried out by heating with hydrochloric acid. In this series twenty per cent. of ethyl alcohol was added to the aqueous hydrochloric acid and resulted in the reaction being more rapidly carried to completion.

PHARMACOLOGICAL TESTS AND RESULTS

Pharmacological Tests and Results.

The local anaesthetic properties of the new compounds were examined in the Department of Pharmacology, University of Edinburgh.

In this investigation the two most generally used techniques for testing local anaesthetics have been employed, (1) the rabbit or guinea-pig corneal test and (2) the intradermal injection method. Each of these methods measures different properties of the drug.

(1). The Rabbit or guinea-pig corneal test.

This method of testing measures two distinct properties of the drug, (a) its power to penetrate the mucous membrane and (b) the power to paralyse nerve endings.

The new compounds prepared in this investigation were tested by the technique originally devised by Sollmann and later modified by Rider (J.Pharmacol., 1930, 39, 329). The eye-lashes of the rabbit were trimmed and the cornea flooded with a solution of the drug in normal saline. The solution was left in contact for five minutes and then washed out with saline. The cornea was tested for the return of the reflex response by lightly touching with a glass rod every three minutes for thirty minutes. At each test the glass rod was applied six times at intervals/

intervals of three to five seconds and the number of times that the rabbit failed to blink was recorded and added up to give an indication of the degree of anaesthesia. Cocaine hydrochloride (one per cent. solution) was used as a reference standard and dilutions of the test solution were made to find a concentration which gave an approximate equal effect to the standard. To overcome the variation of response of different rabbits, four rabbits were used for each test and the standard cocaine solution and the test solution were alternately applied to the same eye.

It was suggested that a more accurate estimation of the local anaesthetic activity could be obtained by a modification of the cross-over technique used by Smith, Fieller and Broom (Quart.J.Pharm., 1944, 17, 108) in the assay of insulin. Two dilutions of the test solution and two dilutions of the standard cocaine solution were made. On the two eyes of one rabbit were applied a high concentration of test solution and a low concentration of standard solution while on the eyes of another rabbit a low concentration of test and a high concentration of standard were applied. From the results, by the use of the appropriate formulae, a comparison of the degree of anaesthesia with the standard, cocaine could be given. Unfortunately the method was not succesful as consistent results could/

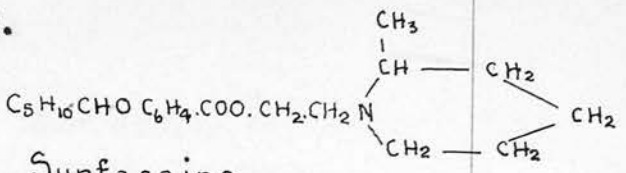
could not be obtained. It had been assumed that the regression lines of the logarithm of the concentration against duration of anaesthesia were parallel as had been shown by Sinha, and Bülbring and Wajda in their intradermal tests (see page 13). It was found on plotting these lines that over a limited range of concentrations the lines for the pyrazolines were parallel. They were not parallel, however, to that for cocaine hydrochloride. Cocaine hydrochloride was therefore not a suitable reference standard for the particular type of local anaesthetic under examination.

Various other local anaesthetics which were known to produce anaesthesia of the mucous membrane were tested and it was found that nupercaine hydrochloride had a regression line which was approximately parallel to that of the pyrazolines being examined (Fig. No.3). Nupercaine hydrochloride was therefore chosen as the reference standard. At low concentrations cocaine and nupercaine do have regression lines which are approximately parallel (Fig. No.3) but at the concentration which is normally used the regression lines are not parallel.

Surfacaine is an analogue of the local anaesthetic Metycaine. From the results as shown in Fig. 3 it has a strong local anaesthetic action on the mucous membrane and a prolonged action

similar/

similar to nupercaine.



Surfacaine

The cornea of the guinea-pig was found to give a more regular response to a stimulus than that of the rabbit. This was in agreement with the findings of Chance and Hunt (J.Pharmacol., 1944, 82, 203) who found that there was no difference in response between the eyes of the guinea-pig and no significant difference in the response between different guinea-pigs.

The local anaesthetic, dissolved in normal saline was dropped by means of a dropping tube into the eye of the guinea-pig which was held in such a position that the cornea was covered by a film of the solution for a period of fifteen seconds. If the guinea-pig blinked during this period the film of solution was renewed. The cornea was tested for the return of the reflex response every five minutes by touching the centre three times with a horse hair attached to a glass rod. The degree of the stimulus was controlled by having the same degree of curvature on the horse hair at each application. The duration of anaesthesia for each concentration was obtained by noting the time when two or more positive responses were obtained from the three stimulations.

The logarithm of the various concentrations of the compounds (as base) was plotted against the duration/

duration of anaesthesia and the results for the four series of compounds under examination are given in Figs. No.4, 5, 6, 7 and are summarised in Tables 11, 12, 13, 14 where the therapeutic values and ratios to Nupercaine are recorded.

From a study of these results it is seen that by the guinea-pig corneal test 1-phenyl-5-(4'-n-propoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate has a therapeutic value of 1.4 and 1-phenyl-5-(4'-n-propoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate a value of 1.0 relative to nupercaine taken as 1.0.

Effect of the secondary amino group substituted in the β-position in the 3-ethyl group of the pyrazoline molecule.

From the results given it is seen that by the guinea-pig corneal test the general effect on the activity of the molecule of the size of the secondary amino group substituted in the β-position in the 3-ethyl group of the pyrazoline molecule is given in the series:-

$$N.Me_2 \langle N.Et_2 \rangle N.C_5H_{10} \rangle N.\text{-}n\text{-}Pr_2 \eqsim N.\text{-}n\text{-}Bu_2 \rangle N.(CH_2)_4O$$

The effect of the morpholino group was considerably to decrease the local anaesthetic activity. A one per cent solution of this drug had no local anaesthetic effect upon the cornea of the guinea-pig.

Effect/

Effect of the alkoxy groups substituted in the phenyl nucleus in position 5 of the pyrazoline molecule.

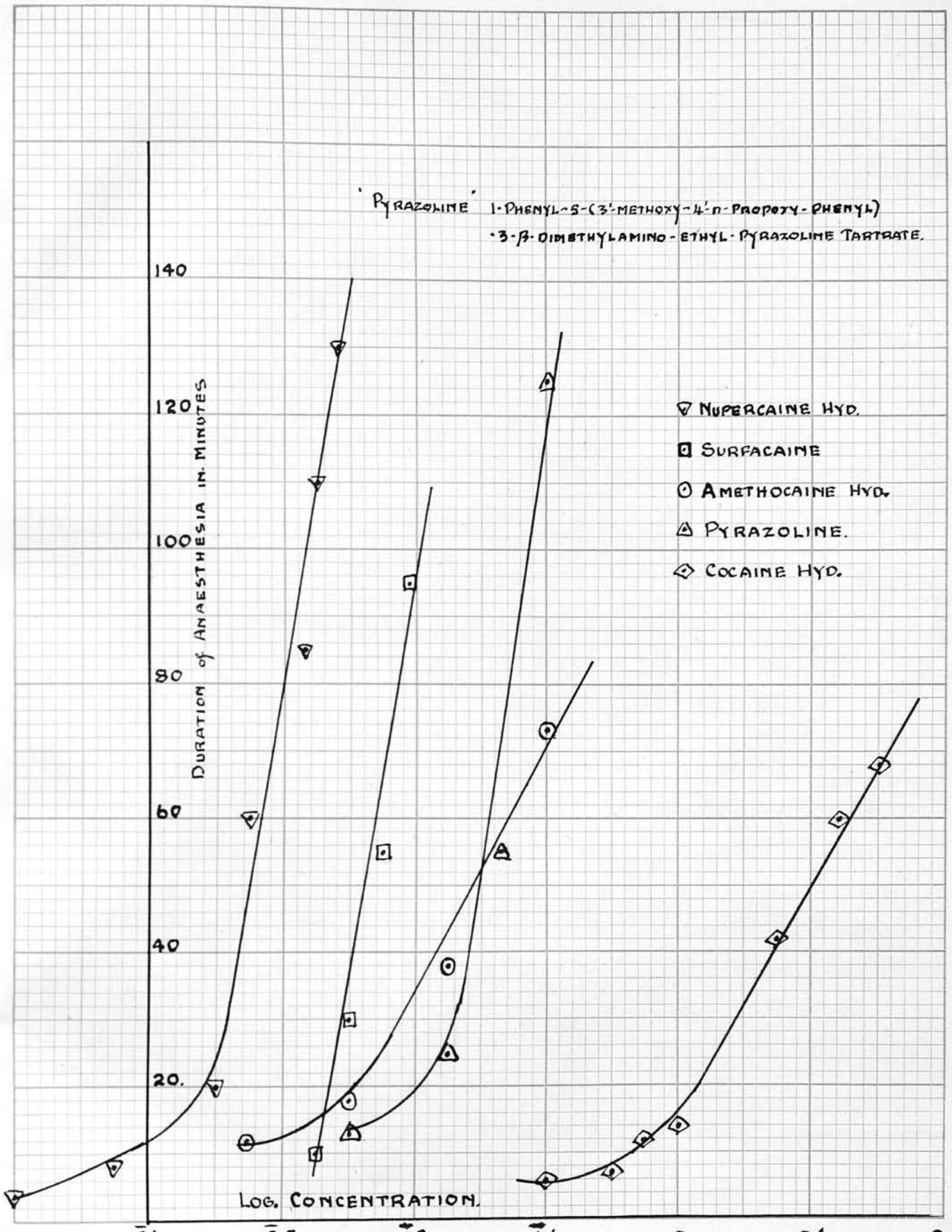
In Fig. 15 the duration of anaesthesia is plotted against the logarithm of the concentration of the diethylamino compounds of the four series having different alkoxy groups substituted in the phenyl nucleus in the 5-position of the pyrazoline molecule. The general effect of the alkoxy groups considered apart from toxicity is given in the series:-

n-propoxy > n-butoxy > methoxy-n-propoxy > methoxy-n-butoxy

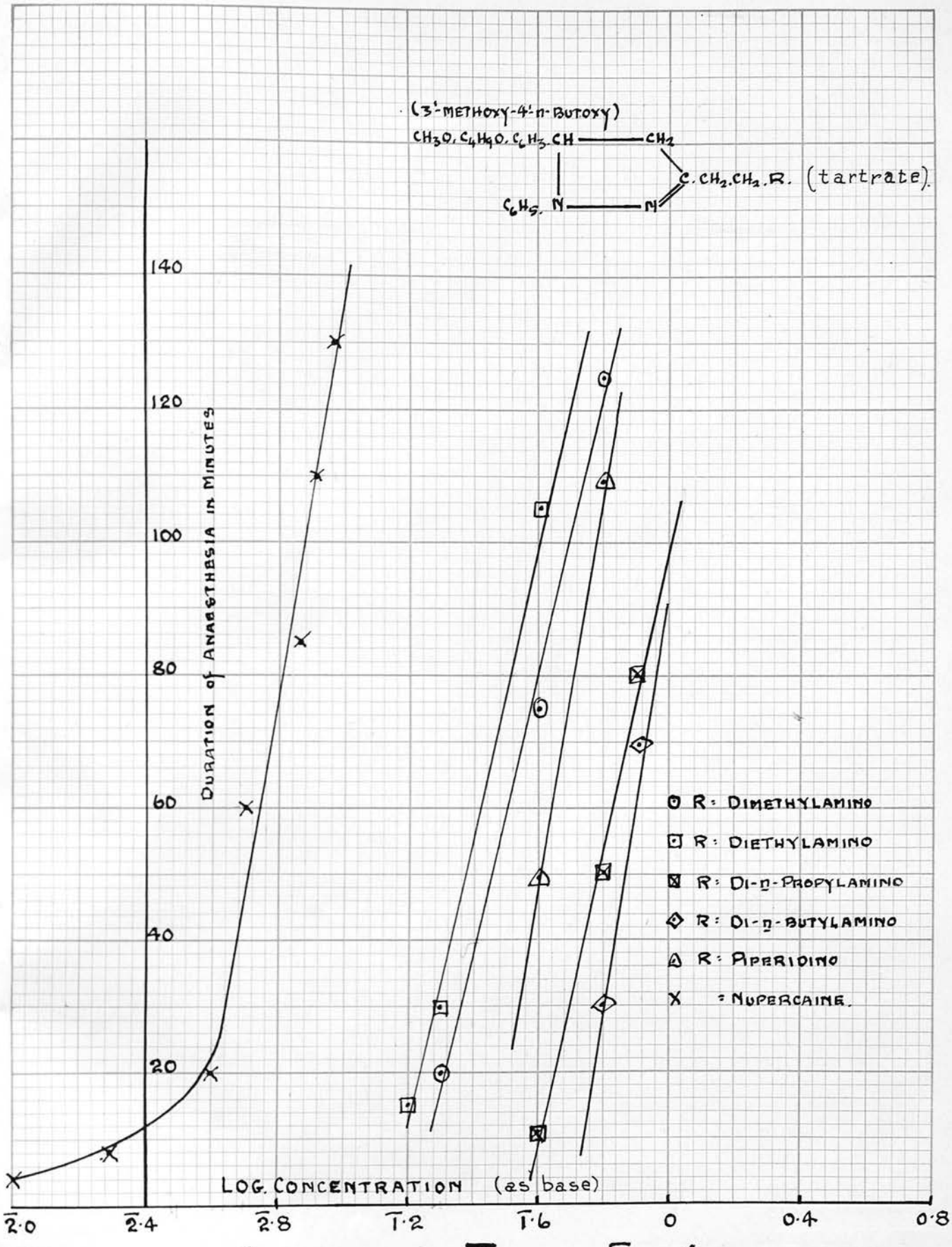
As shown in Figs. 4, 5, 6, 7 the observation first made by Sinha (J.Pharmacol., loc.cit.) that there exists a linear relationship between the duration of anaesthesia and the logarithm of the concentration has again been confirmed.

Irritation.

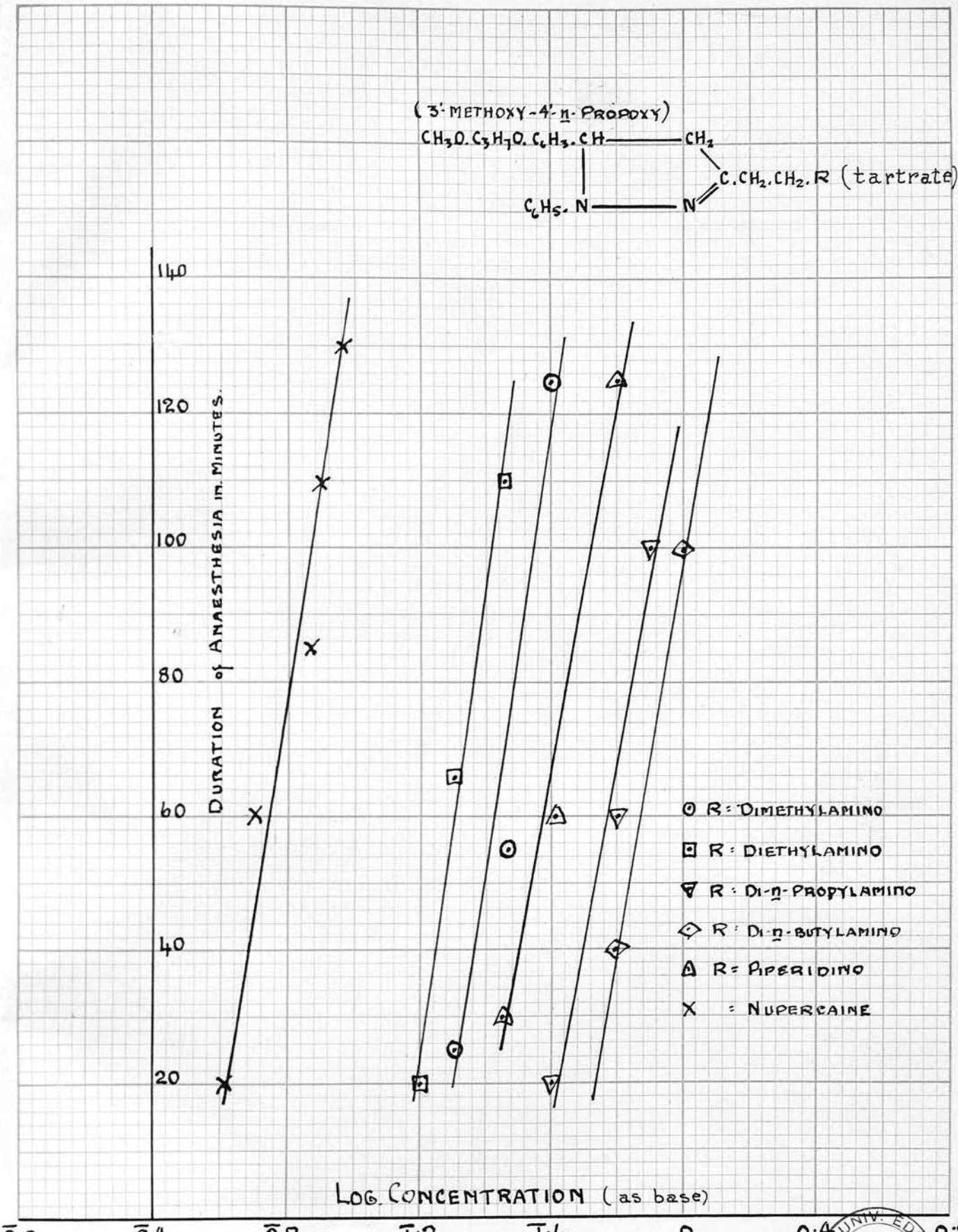
There was evidence of some irritation to the eye of the guinea-pig caused by the pyrazoline compounds.



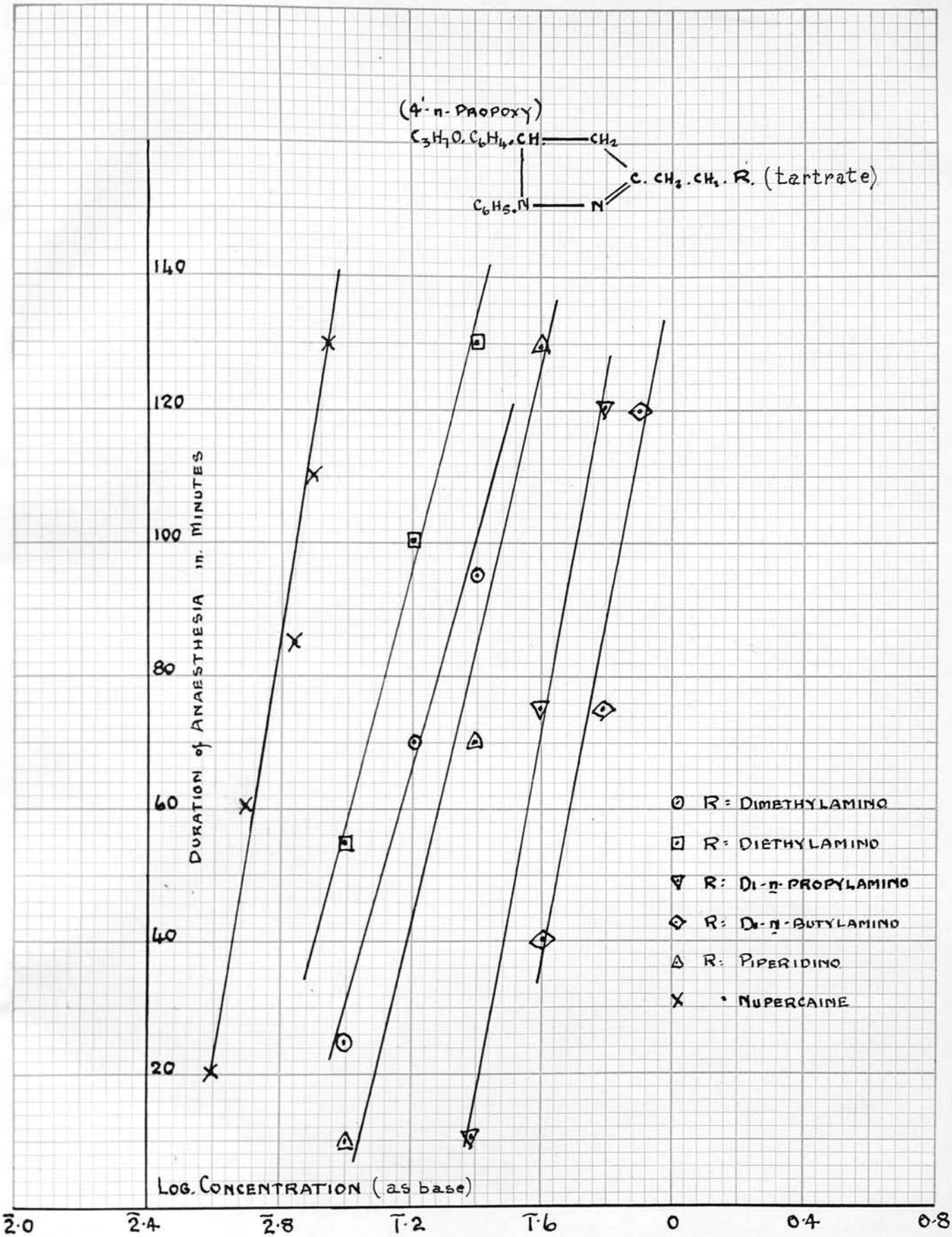
CORNEAL TEST FIG. 3



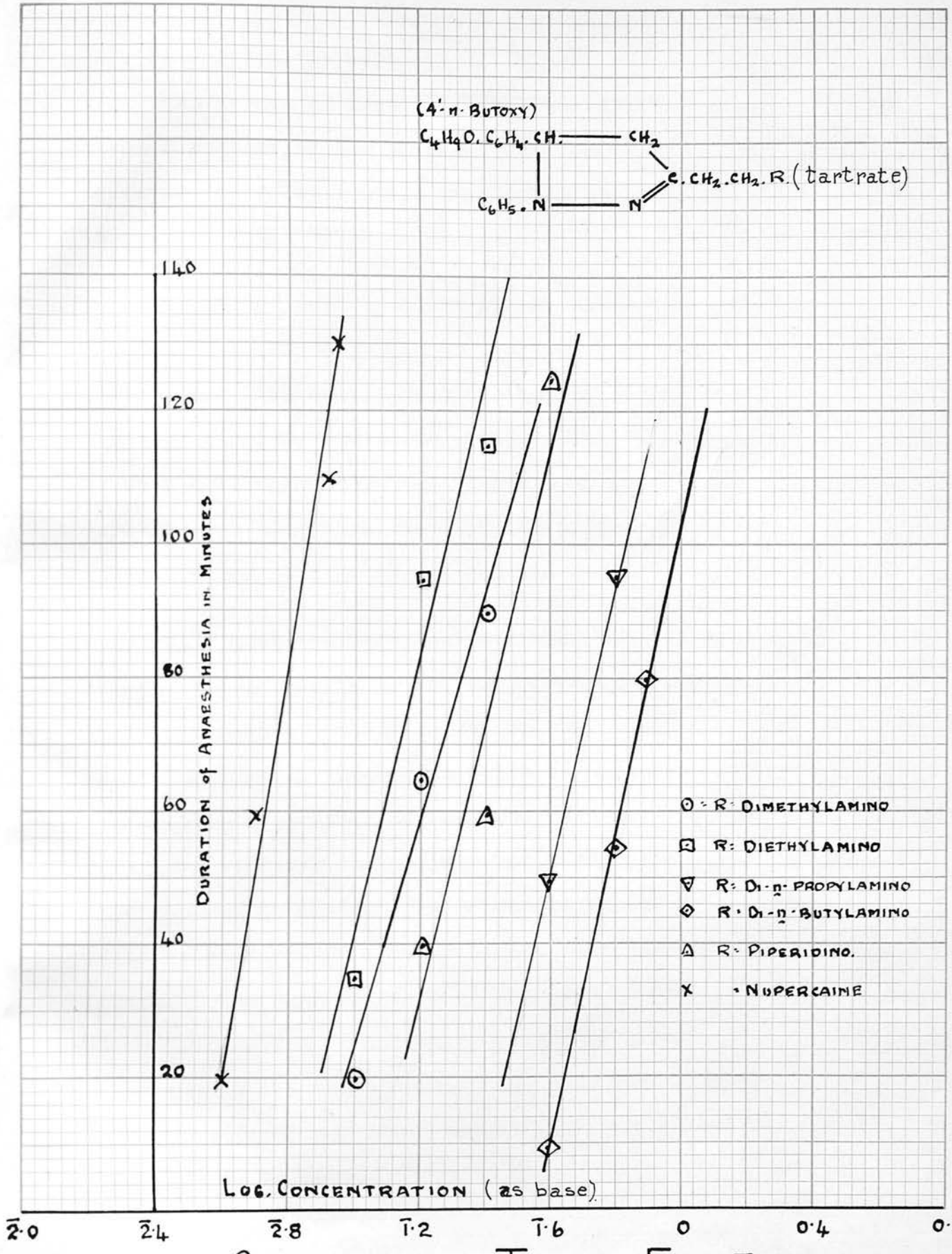
CORNEAL TEST FIG. 4



CORNEAL TEST FIG. 5



CORNEAL TEST FIG. 6



CORNEAL TEST FIG. 7

(2). Intradermal injection.

This method of testing local anaesthetics gives a measure of the power of the drug to paralyse the nerve endings unaffected by its power to penetrate the mucous membrane.

The method used by Sinha (Ibid., 1936, 57, 199) was to inject the solution of the drug into the human arm. The shaved back of the guinea-pig was found by Bülbring and Wajda (Ibid., 1945, 85, 78) to be a more convenient and accurate method of carrying out this test, and for the purpose of this investigation this latter method was used.

Fully grown guinea-pigs were used for the test and on the day preceding the experiment the backs of the animals were clipped and shaved. This caused some local irritation which disappeared overnight. Procaine hydrochloride was used as the reference standard as Bülbring and Wajda (loc.cit.) have shown that cocaine hydrochloride is not a suitable standard on account of its vasoconstrictor action. The sensitiveness of the skin of the guinea-pig varies from back to front being more sensitive in the front area. For this reason each concentration of the local anaesthetic was tested in four different positions.

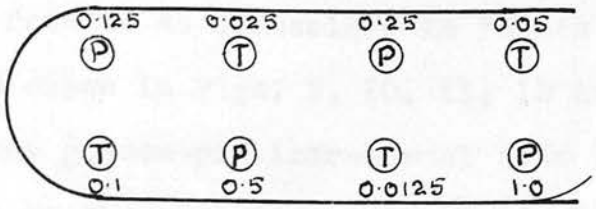
Four guinea-pigs were used for each test and

four/

four concentrations of the test solution and of the standard were injected intradermally along each side of the mid-line (Fig. 8). The same concentrations of the test and the standard were injected into each of the guinea-pigs but in each case the site of each injection was altered (Fig. 8). The wheal formed by each injection was outlined in ink and after observing the animals normal reaction to the pin-prick, the marked area was tested six times at intervals of three to five seconds. The test was applied every five minutes for thirty minutes and the number of pricks failing to elicit a response were added up for each concentration (Tables No. 6, 7, 8, 9) and out of a possible thirty-six gave an indication of the degree of anaesthesia. The mean value of the four readings was plotted against the logarithm of the concentration of the drug, as base, and the results for the four series of compounds under examination are given in Figs. 9, 10, 11, 12 and the therapeutic values and ratios to procaine are summarised in Tables 11, 12, 13 14.

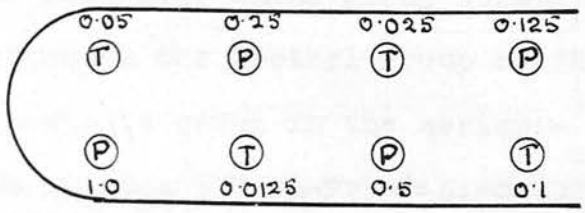
From the results given it is seen that 1-phenyl-5-(4'-n-propoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate has a therapeutic value of 4.2 and 1-phenyl-5-(4'-n-propoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate has a value of 3.7 compared with procaine, 1.0.

Effect/



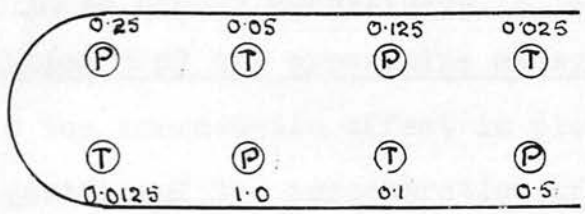
Head

Guinea-pig No.1



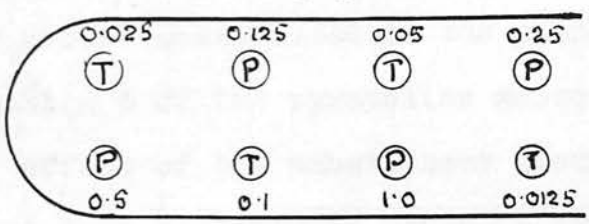
Head

Guinea-pig No.2



Head

Guinea-pig No.3



Head

Guinea-pig No.4

Figure No. 8. Position of the intradermal injections on the shaved back of the guinea-pig. P = procaine hydrochloride and T = solution of the test drug.

Effect of the secondary amino group substituted in the β-position in the 3-ethyl group of the pyrazoline molecule.

From the results as summarised in Tables 11, 12, 13, 14 and shown in Figs. 9, 10, 11, 12 it is seen that by the guinea-pig intradermal test the general effect on the activity of the molecule of the size of the secondary amino group substituted in the β position in the 3-ethyl group of the pyrazoline molecule is given in the series:-

$$N.Me_2 \left\langle N.Et_2 \backsimeq N.C_5H_{10} \right\rangle N.\text{-}n\text{-}Pr_2 \backsimeq N.\text{-}n\text{-}Bu_2 \rangle \; N.(CH_2)_4O$$

Effect of the alkoxy groups substituted in the phenyl nucleus in position 5 of the pyrazoline molecule.

In Fig. 16 the anaesthetic effect is plotted against the logarithm of the concentration of the diethylamino compounds of the four series having varying alkoxy groups substituted in the phenyl nucleus in position 5 of the pyrazoline molecule. In general the effect of the substituent groups considered apart from toxicity is given in the series:-

n-propoxy $\rangle$ methoxy-n-propoxy $\rangle$ n-butoxy $\rangle$ methoxy-n-butoxy

Irritation.

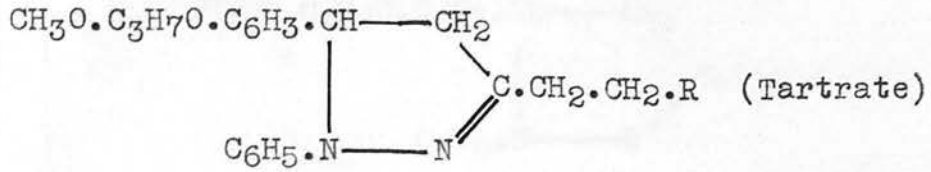
When the compounds were injected into the guinea-pigs they appeared to cause more irritation than the injection of procaine hydrochloride.

As/

As shown in Figs. 9, 10, 11, 12 the observation first made by Sinha (J.Pharmacol., loc.cit.) that a linear relationship exists between the local anaesthetic effect and the logarithm of the concentration has again been confirmed.

TABLE No. 6.

Intradermal test in guinea-pigs.



3'-Methoxy-4'-n-propoxy substituted in the phenyl nucleus attached to the 5 position of the pyrazoline molecule.

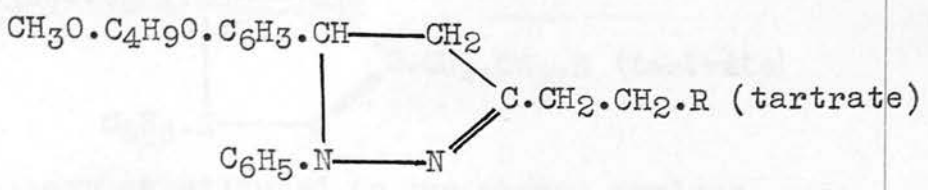
Number of pricks (out of 36) with mean values, failing to elicit a response after intradermal injection of the drug in guinea-pigs.

Concentration gm.% w/v	0.1	0.05	0.025	0.0125
R = Dimethylamino	26 24 33 m= 24 14	18 16 m= 16 15	15 5 m= 10 9	4 3 m= 3 2
R = Diethylamino	30 32 m= 31 28 33	25 24 m= 23 21	13 18 m= 16 13 19	8 12 m= 8 5 7
R = Di-n-propyl-amino	16 13 m= 18 24 17	13 10 m= 11 8 16	5 8 m= 5 4 4	
R = Di-n-butyl-amino	31 25 m= 21 6	15 21 m= 15 10	9 8 m = 7 4	
R = Piperidino	31 25 32 m= 28 32	34 15 20 m= 21 16	16 18 11 m= 13 8	8 8 4 m= 5 2
R = Morpholino	18 7 m= 13 14	10 5 m= 6 5		

Concentration gm.% w/v.	0.5	0.25	0.125
Procaine Hyd.	m = 27	m = 20	m = 11

TABLE No. 7.

Intradermal test in guinea-pigs.



3'-Methoxy-4'-n-butoxy substituted in the phenyl nucleus attached to the 5 position of the pyrazoline molecule.

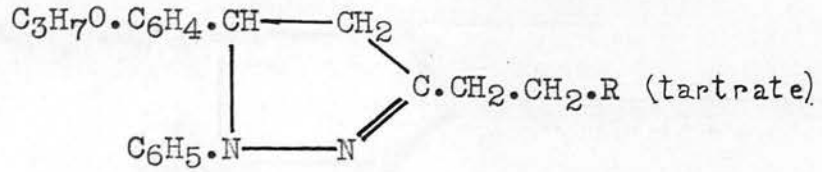
Number of pricks (out of 36) with mean values, failing to elicit a response after intradermal injection of the drug in guinea-pigs.

Concentration gm.% w/v.	0.2	0.1	0.05	0.025
R = Dimethylamino	30 24 26 m= 26 23	22 18 28 m= 23 24	13 16 10 m= 12 9	6 3 2 5
R = Diethylamino	34 30 m= 32 28 35	24 22 m= 27 31 32	20 15 m= 17 20 14	12 8 m= 10 14 7
R = Di-n-propyl-amino	17 21 23 m= 20 20	14 16 19 m= 14 17	7 8 12 m= 8 6	
R = Di-n-butyl-amino	24 20 27 m= 24 24	12 15 17 m= 16 19	11 10 7 m= 9 7	
R = Piperidino	28 32 33 m= 30 26	28 22 20 m= 24 25	13 15 20 m= 16 17	5 6 8 m= 7 10
R = Morpholino	20 17 12 m= 16 16	10 15 13 m= 13 12	6 7 3 m= 5 5	

Concentration gm.% w/v. Procaine Hyd.	0.5	0.25	0.125
	m = 28	m = 22	m = 12

TABLE No. 8.

Intradermal test in guinea-pigs.



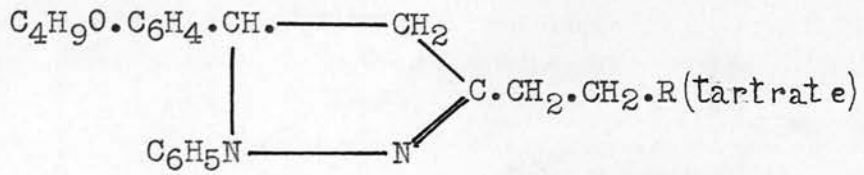
4'-n-Propoxy substituted in the phenyl nucleus attached to the 5 position of the pyrazoline molecule.

Number of pricks (out of 36) with mean values, failing to elicit a response after intradermal injection of the drug in guinea-pigs.

Concentration gm.% w/v.	0.1	0.05	0.025	0.0125
R = Dimethylamino	31 26 25 m= 28 31	17 25 19 m= 20 17	12 8 10 m= 9 7	1 6 4 m= 4 3
R = Diethylamino	36 35 m= 35 36 34	29 22 m= 24 24 22	22 18 m= 16 12 14	12 7 m= 9 8 9
R = Di-n-propyl-amino	26 16 20 m= 21 22	13 11 7 m= 10 10	1 6 2 m= 4 7	
R = Di-n-butyl-amino	14 20 18 m= 18 19	10 13 6 m= 9 7	0 6 2 m= 3 5	
R = Piperidino	34 32 m= 32 26 34	22 18 m= 21 18 27	16 18 m= 14 9 15	6 2 m= 5 4 9
Concentration gm.% w/v.	0.5	0.25	0.125	
Procaine Hyd.	m = 31	m = 20	m = 10	

TABLE No. 9.

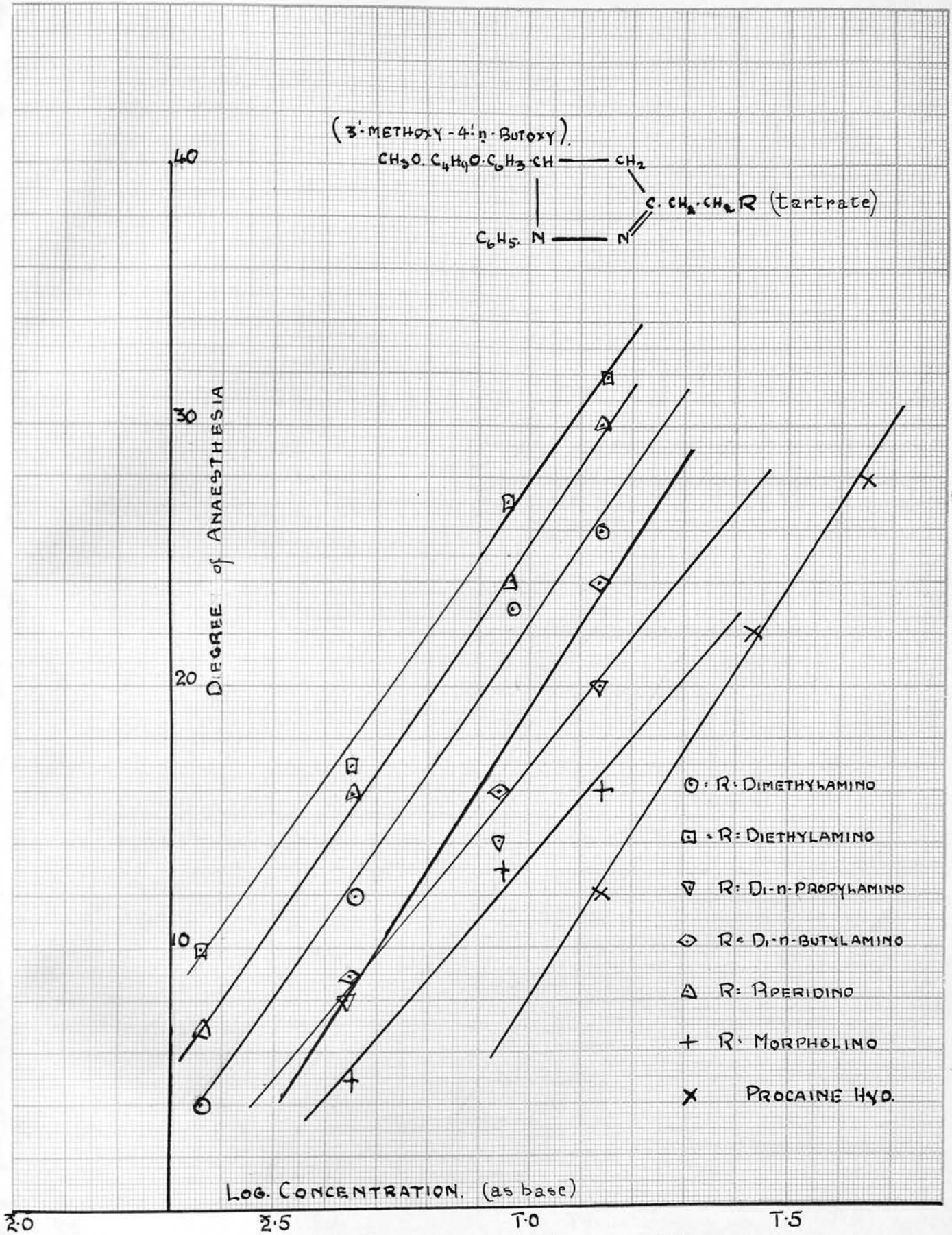
Intradermal tests in guinea-pigs.



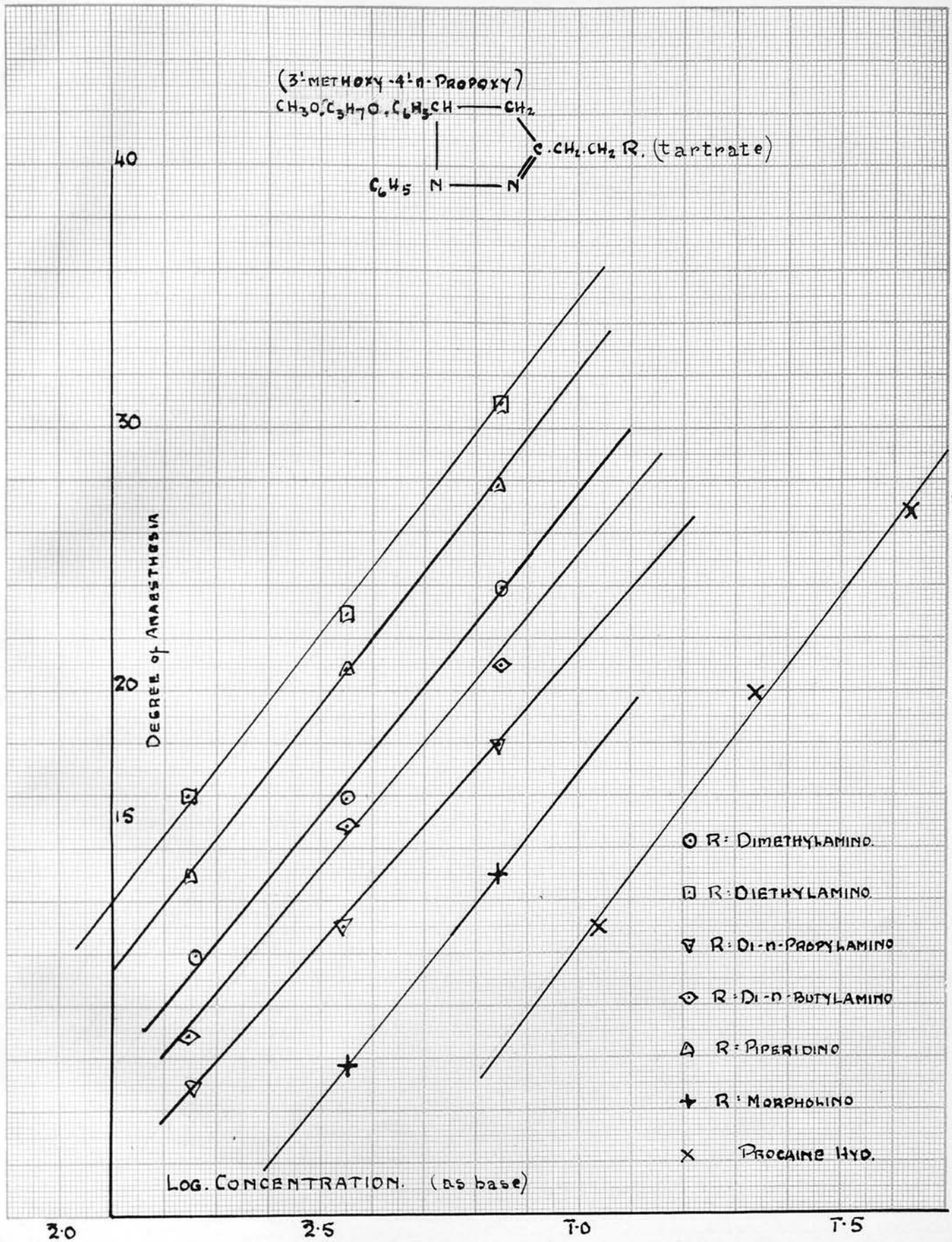
4'-n-butoxy substituted in the phenyl nucleus attached to the 5 position of the pyrazoline molecule.

Number of pricks (out of 36) with mean values, failing to elicit a response after intradermal injection of the drug in guinea-pigs.

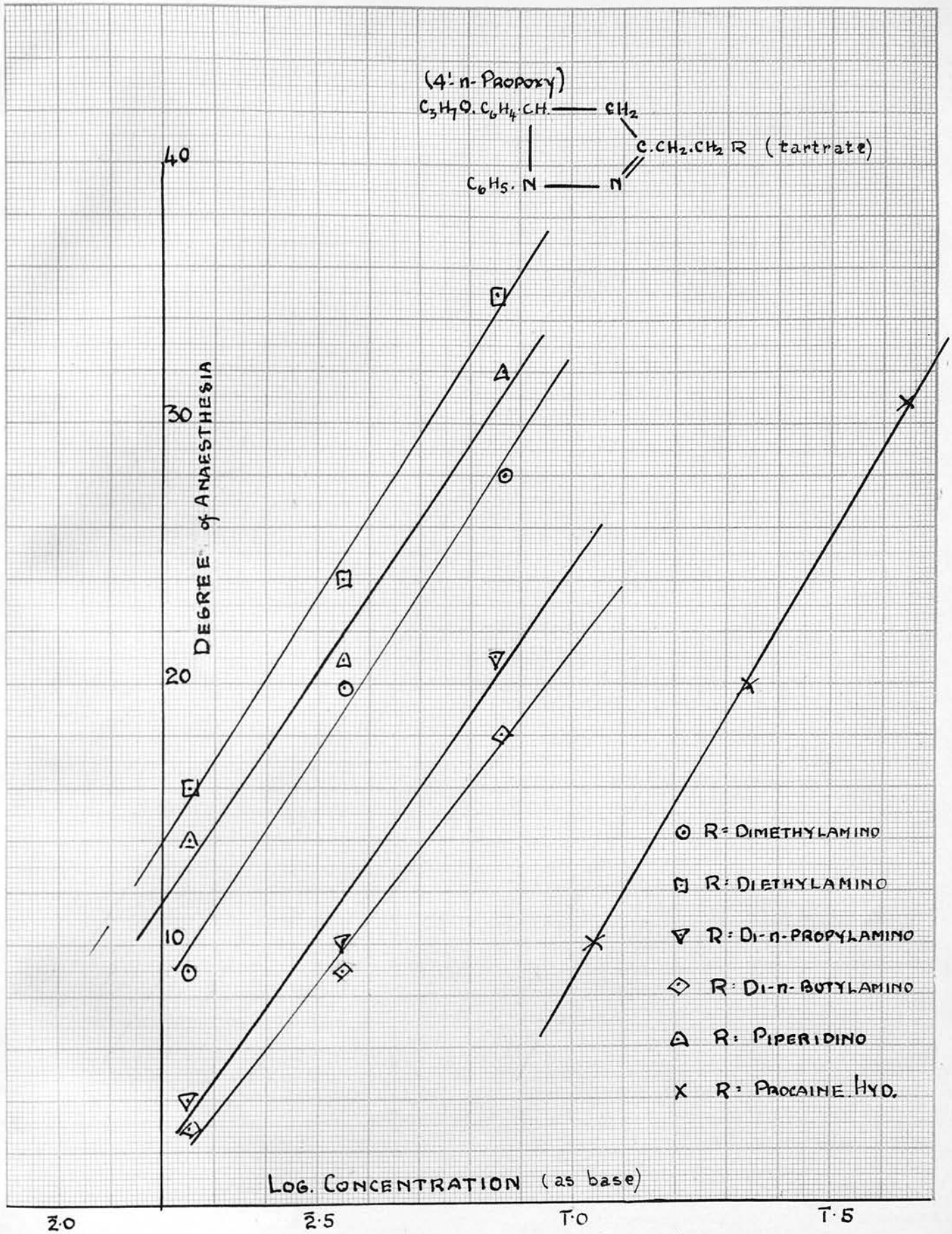
Concentration gm.% w/v.	0.1	0.05	0.025	0.0125
R = Dimethylamino	31 25 20 m= 26 29	18 15 11 m= 15 17	5 6 9 m= 7 8	
R = Diethylamino	35 36 m= 33 28 34	24 19 m= 22 18 28	10 14 m= 12 16 9	2 6m = 3 4 1
R = Di-n-propyl-amino	23 19 17 m= 20 22	13 10 6 m= 9 8		
R = Di-n-butyl-amino	19 13 16 m= 17 21	6 7 11 m= 7 3		
R = Piperidino	36 31 24 m= 30 29	15 13 24 m= 18 22	13 8 9 m= 10 12	
Concentration gm.% w/v.	0.5	0.25	0.125	
Procaine Hyd.	m = 32	m = 22	m = 12	



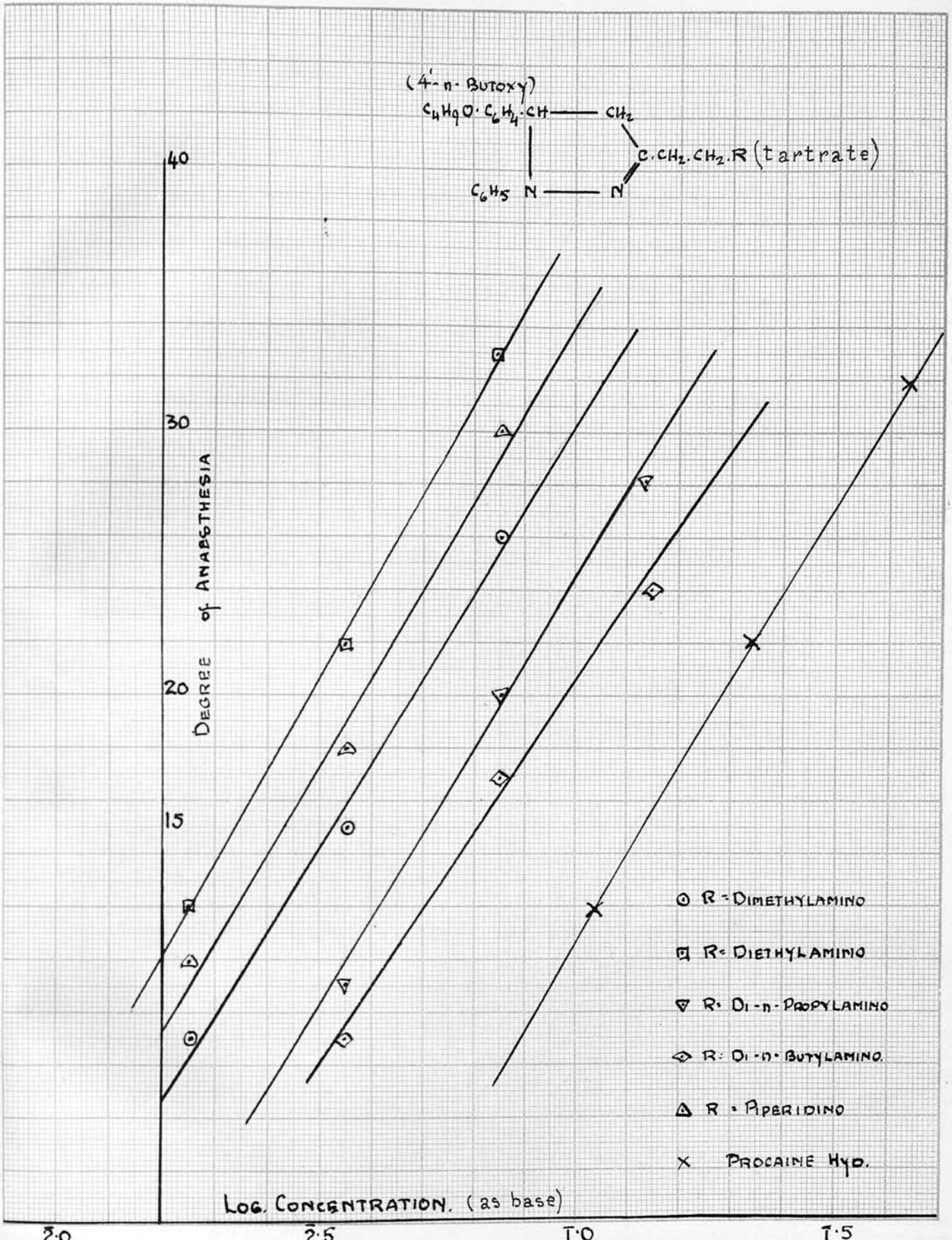
INTRADERMAL TEST FIG. 9



INTRADERMAL TEST FIG. 10



Intradermal Test. Fig. 11



INTRADERMAL TEST FIG 12

(3). Toxicity tests.

The median lethal dose of the new compounds was estimated by intraperitoneal injection in mice. There was no evidence of convulsions as given by cocaine hydrochloride but there was evidence of a delayed action which caused deaths thirty-six to forty-eight hours after injection.

The results of the toxicity tests are given in Table 10 and in Figs. 13, 14, the percentage mortality is plotted against the dose (mg.).

Effect of alkoxy groups substituted in the phenyl nucleus in position 5 of the pyrazoline molecule.

In Fig. 13 are plotted the percentage mortality against the dose (mg.) of the piperidino compounds of the four series of pyrazolines under examination and it is shown that the general effect of the size of the alkoxy groups is given in the series:-

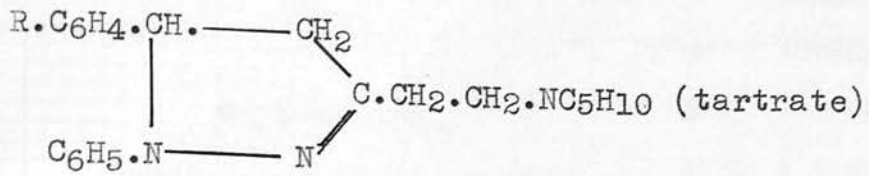
n-propoxy < n-butoxy < methoxy-n-propoxy < methoxy-n-butoxy

Effect of the secondary amino group substituted in the β position in the 3-ethyl group of the pyrazoline molecule.

A full investigation of the effect of this group was not carried out but from the estimation of the toxicity of two compounds from the same series it is shown that the diethylamino compound is more toxic than the piperidino compound, Fig.14.

TABLE No.10.

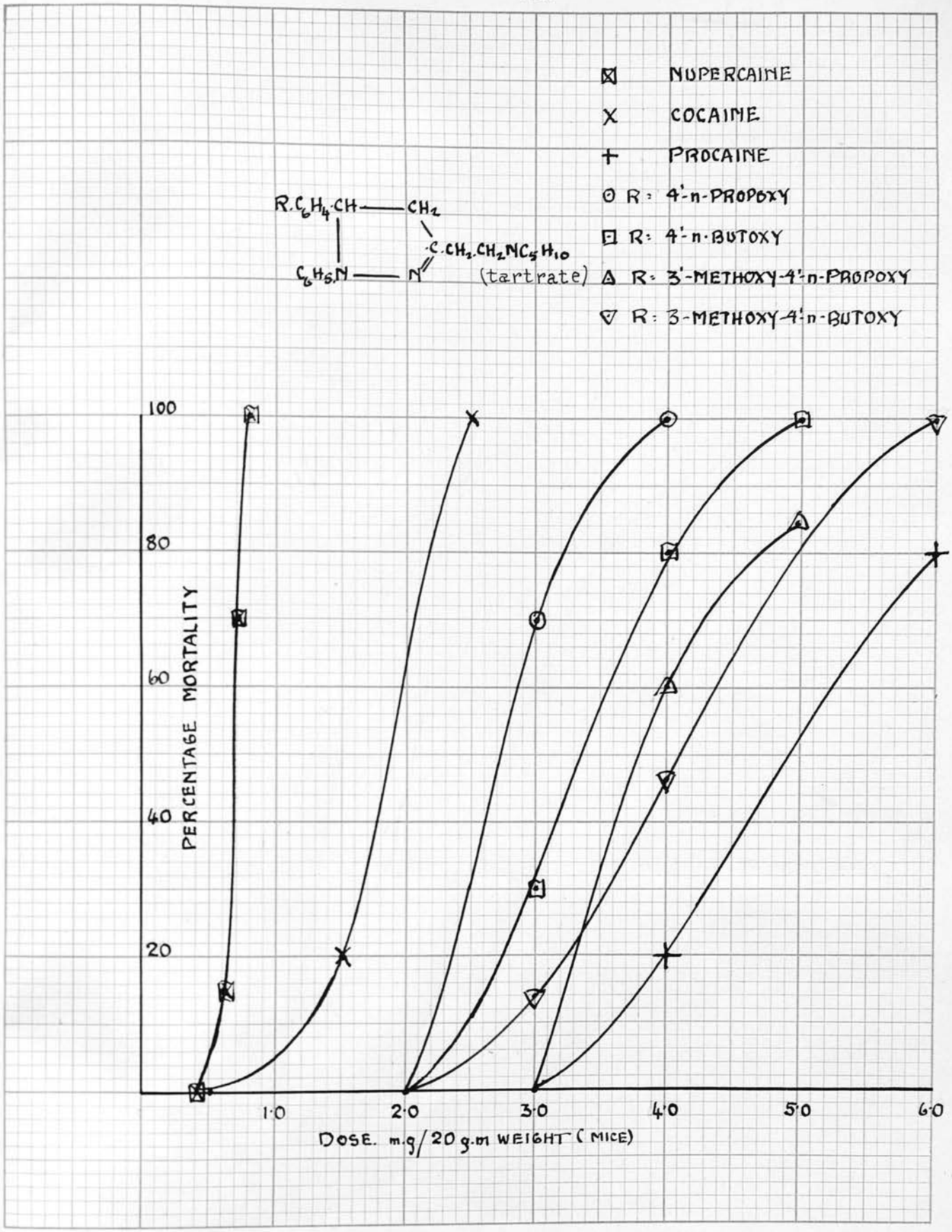
Toxicity tests in Mice.



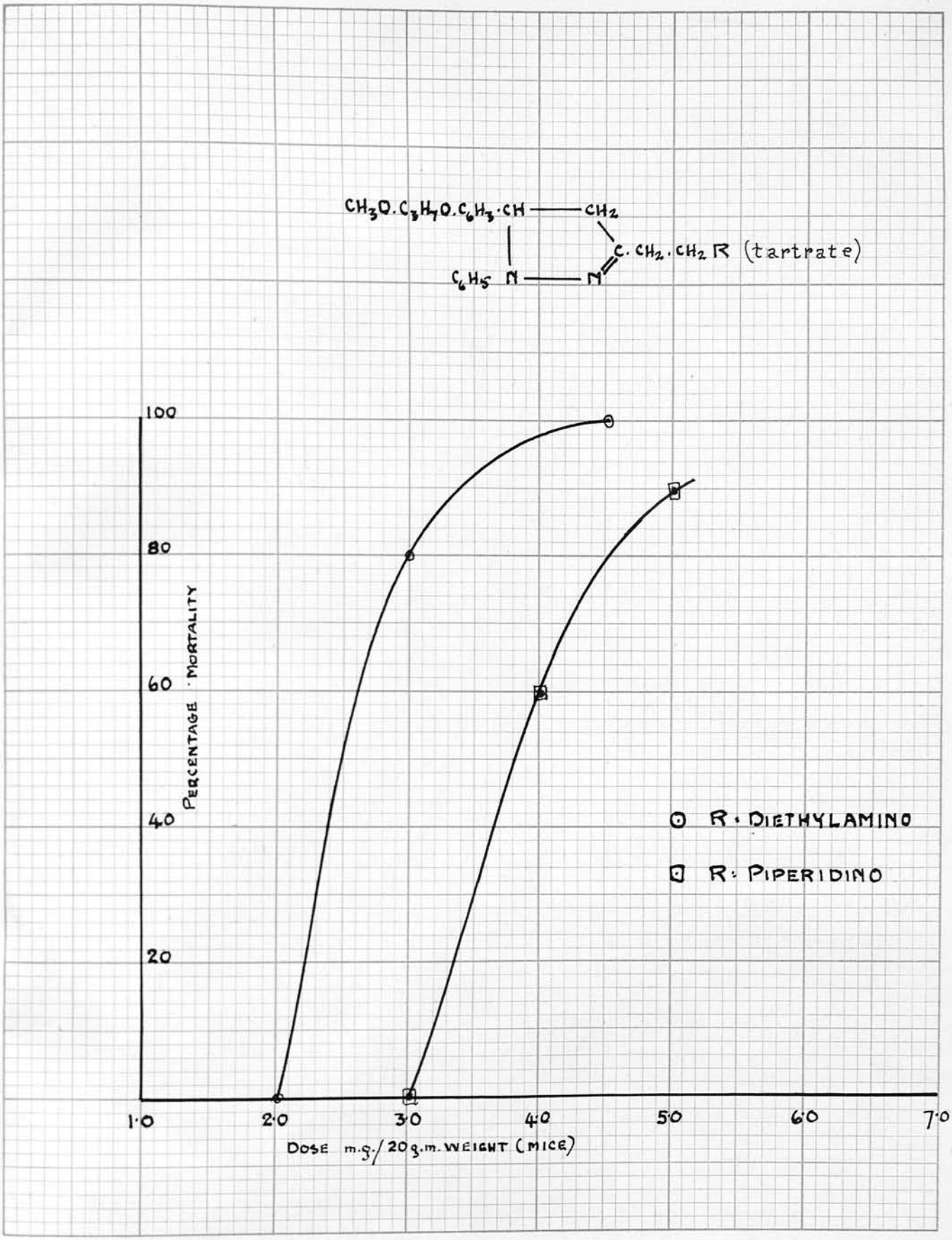
The toxicities were estimated by intraperitoneal injection in mice.

Final readings taken at 48 hours after injection.

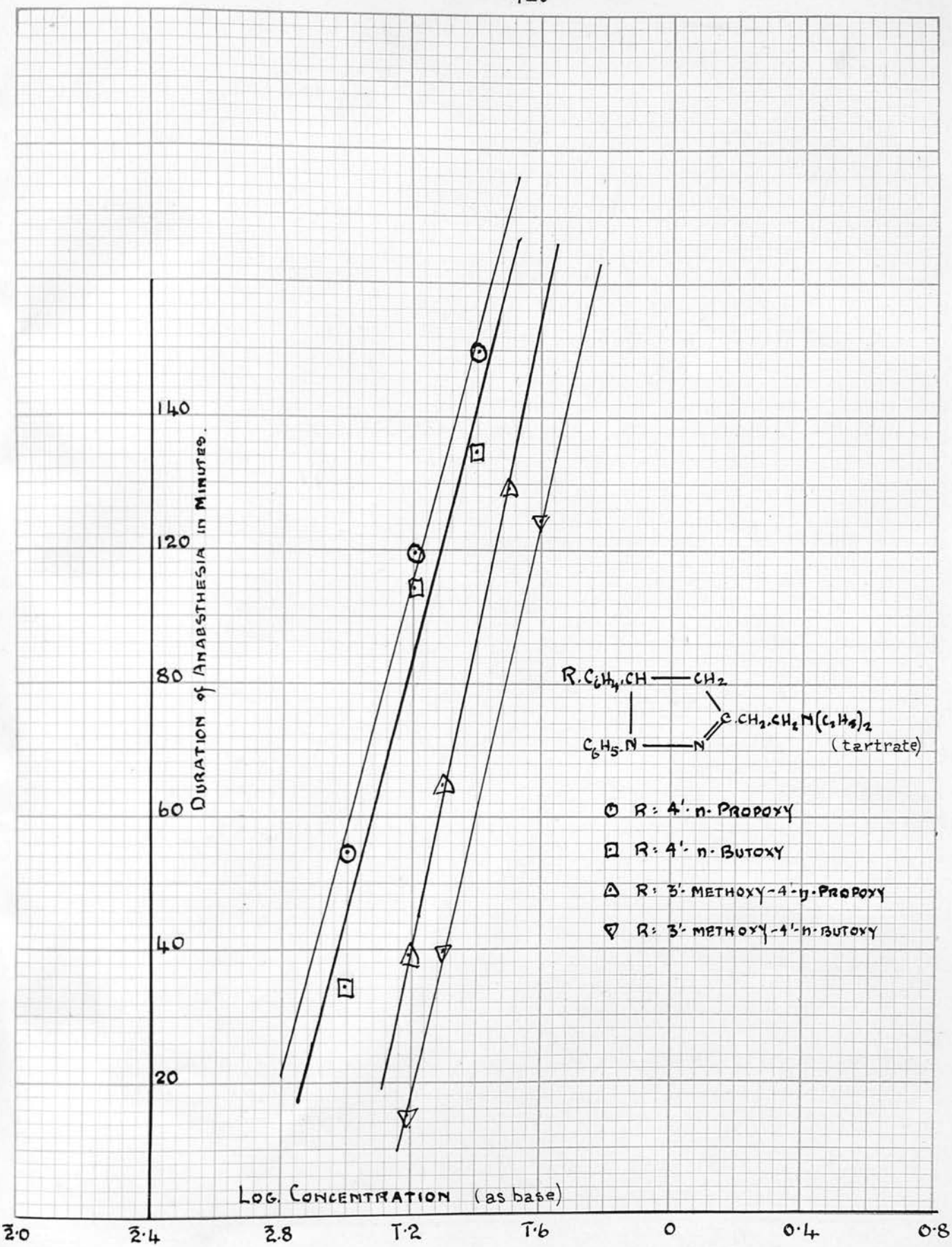
Drug	Dose mg./20 gm.	Number of mice injected	Number of deaths	Mortality %	L.D.50 mg./kg.
R = 3'-methoxy--4'-n-propoxy.	2.0	7	0	0	170
	3.0	7	0	0	
	4.0	7	4	60	
	5.0	7	6	85	
R = 3'-methoxy--4'-n-butoxy	1.0	7	0	0	205
	2.0	7	0	0	
	3.0	7	1	15	
	4.0	7	3	43	
	6.0	7	7	100	
R = 4'-n-propoxy	1.0	7	0	0	135
	2.0	7	0	0	
	3.0	7	5	70	
	4.0	7	7	100	
	5.0	7	7	100	
R = 4'-n-butoxy	3.0	7	2	30	165
	4.0	7	6	80	
	5.0	6	6	100	
	6.0	6	6	100	
Nupercaine Hyd.	0.4	6	0	0	35
	0.5	7	0	0	
	0.6	6	1	18	
	0.7	7	5	70	
	0.8	7	7	100	
Procaine Hyd.	1.0	10	0	0	225
	2.0	10	0	0	
	4.0	20	8	40	
	6.0	10	8	80	
	8.0	20	20	100	
Cocaine Hyd.	1.0	10	2	20	110
	1.5	10	2	20	
	2.0	10	2	20	
	2.5	10	10	100	



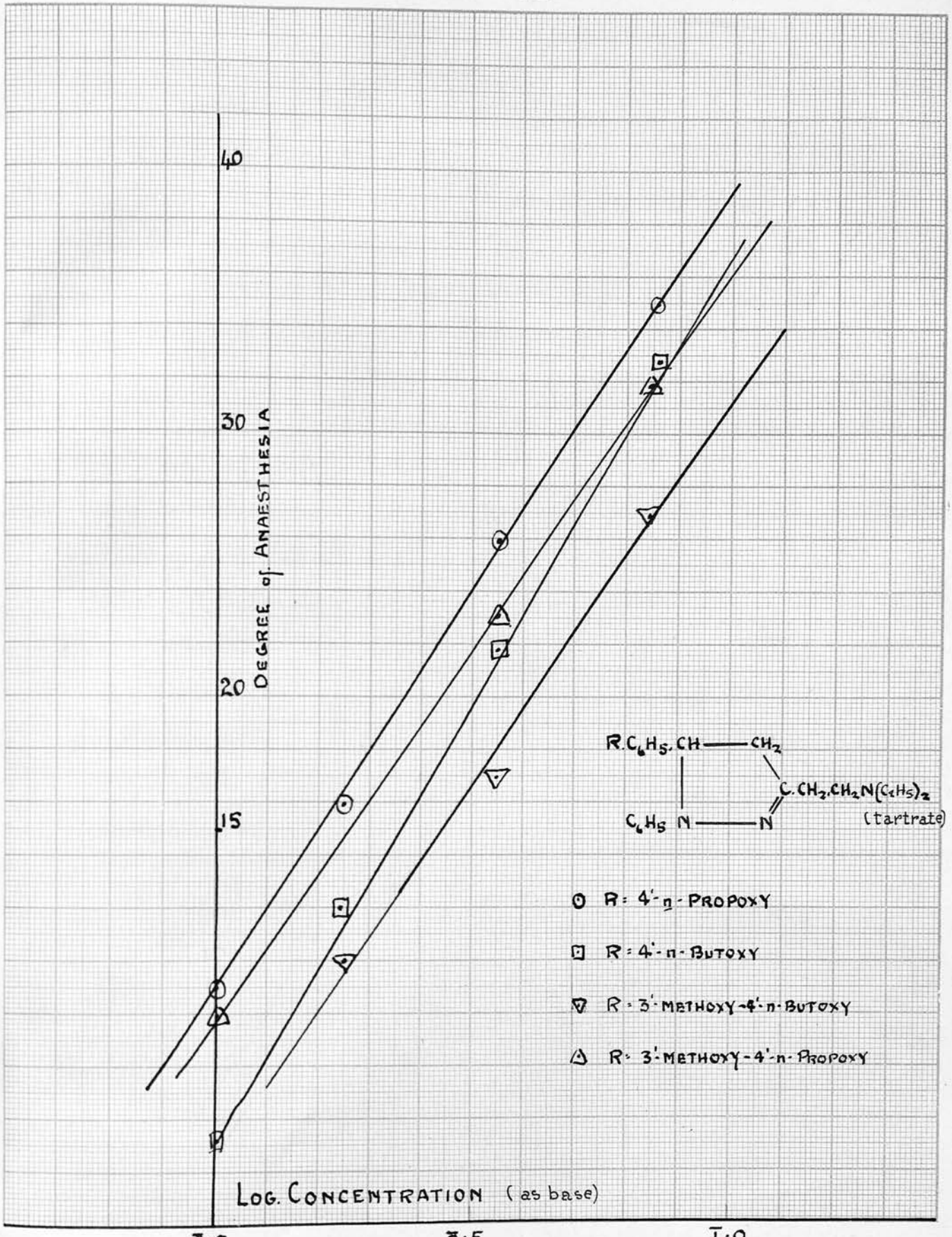
TOXICITY TEST FIG. 13



TOXICITY TEST FIG. 14



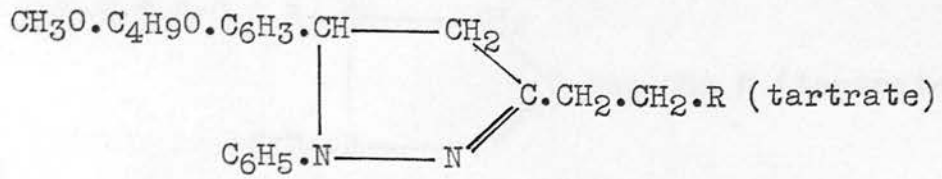
CORNEAL TEST FIG. 15



INTRADERMAL TEST FIG. 16

TABLE No. 11.

Summary of the pharmacological tests.

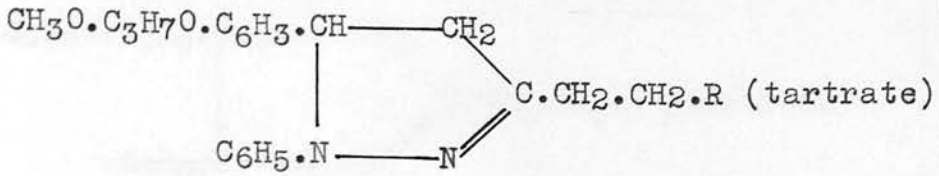


3'-Methoxy-4'-n-butoxy substituted in the phenyl group attached to position 5 of the pyrazoline molecule.

	Guinea Pig Wheal		Guinea Pig Cornea		Toxicity
	Ratio to procaine	Therapeutic Value	Ratio to Nupercaine	Therapeutic Value	L.D.50(mice) mg./kg.
R = Dimethylamino	3.3		0.15		
R = Diethylamino	5.0	3.3	0.20	0.85	(150)
R=Di-n-propylamino	1.8		0.08		
R=Di-n-butylamino	2.0		0.06		
R = Piperidino	5.0	4.5	0.1	0.5	205
R = Morpholino	1.5		-		
Procaine Hyd.	1.0				225
Nupercaine			1.0		35
Cocaine Hyd.					110

TABLE No.12.

Summary of the pharmacological tests.

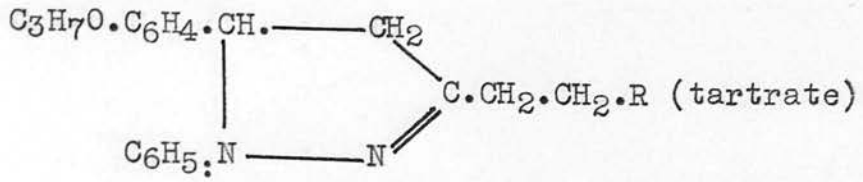


3'-Methoxy-4'-n-propoxy substituted in the phenyl group attached to position 5 of the pyrazoline molecule.

	Guinea Pig Wheal		Guinea Pig Cornea		Toxicity
	Ratio to procaine	Therapeutic Value	Ratio to Nupercaine	Therapeutic Value	L.D.50(Mice) mg./kg.
R = Dimethylamino	4.0		0.15		
R = Diethylamino	7.0	3.5	0.25	0.9	(125)
R=Di-n-propylamino	2.5		0.06		
R=Di-n-butylamino	3.5		0.05		
R=Piperidino	6.0	4.5	0.1	0.5	170
R=Morpholino	1.5		-		
Procaine hyd.	1.0				225
Nupercaine Hyd.			1.0		35
Cocaine Hyd.					110

TABLE No.13.

Summary of the pharmacological tests.



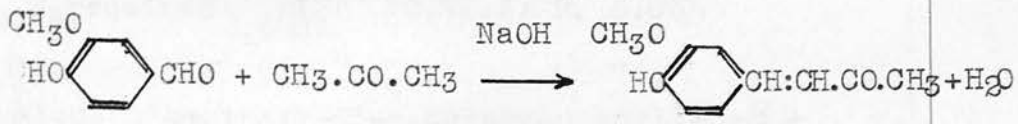
4'-n-Propoxy substituted in the phenyl group attached to position 5 of the pyrazoline molecule.

	Guinea Pig Wheal		Guinea Pig Cornea		Toxicity
	Ratio to Procaine	Therapeutic Value	Ratio to Nupercaine	Therapeutic Value	L.D.50(Mice) mg./kg.
R = Dimethylamino	5.5		0.35		
R = Diethylamino	8.5	3.7	0.50	1.4	(98)
R=Di-n-propylamino	3.0		0.15		
R=Di-n-butylamino	2.5		0.10		
R=Piperidino	7.0	4.2	0.25	1.0	135
Procaine Hyd.	1.0				225
Nupercaine Hyd.			1.0		35
Cocaine Hyd.					110

E X P E R I M E N T A L

(1) β-Amino-ketones and related pyrazolines derived from m-methoxy-p-n-butoxy-benzylidene-acetone.

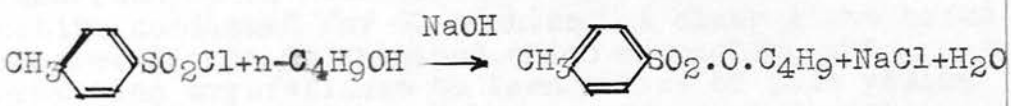
Vanillidene-acetone (Harries, Ber., 1891, 24, 3180)



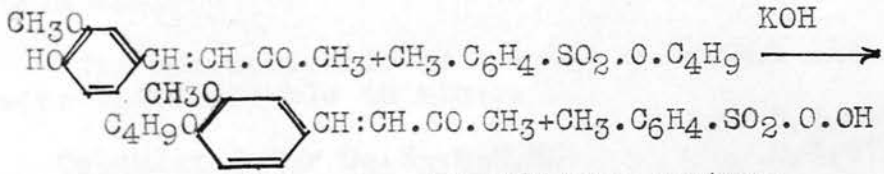
124 gm. Vanillin
500 ml. acetone
170 ml. 50% sodium hydroxide solution

The vanillin is dissolved in the acetone contained in a litre flask and the sodium hydroxide solution added gradually. The contents of the flask turned solid and are brought into solution by heating on the steam-bath under reflux for five minutes. The dark reddish solution is allowed to stand at room temperature for forty-eight hours during which crystallisation takes place. The solid is again brought into solution by heating and the solution made faintly acid with acetic acid and most of the excess acetone removed by distillation. A dark reddish oil separates which crystallises on cooling to a mass of reddish crystals. The solid is filtered off, washed with water, dried and re-crystallised from acetone to give pale yellow crystals. m.pt. 128°-129°C. Yield 70%.

n-Butyl-p-Toluenesulphonate (Organic Syn., Vol., IX, 29)



m-Methoxy-p-n-butoxy-benzylidene acetone



192 gm. vanillidene acetone
228 gm. n-butyl-p-toluenesulphonate
70 gm. potassium hydroxide

The vanillidene acetone is dissolved in the alcohol by gently heating on a water-bath and the n-butyl-p-toluenesulphonate added. The potassium hydroxide dissolved in the minimum of water is added and the mixture heated under reflux on the water-bath for 1½ hours. The solution is then poured into 5000 ml. of water when a dark coloured oil separates and crystallises on cooling. The solid is removed by filtration, washed with water, dried and recrystallised from acetone to give pale yellow crystals. m.pt. 79°-80°C. Yield 76%.

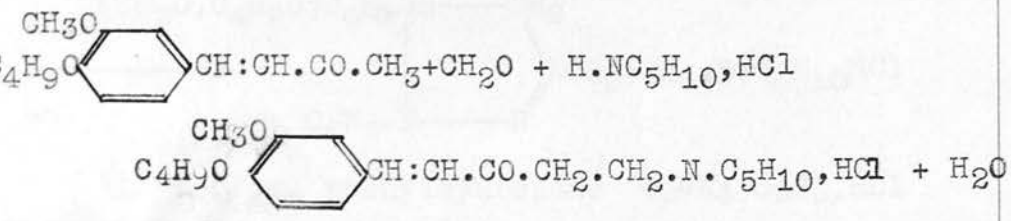
The /

The compound is soluble in alcohol, slightly soluble in ether, but insoluble in water.

	Found:	C,72.3; H, 7,94%
$C_{15}H_{20}O_3$ requires	:	C,72.6; H, 8.06%

1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline hydrochloride.

(a) 1-Piperidino-5-(3'-methoxy-4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



6.2 gm. m-methoxy-p-n-butoxybenzylidene acetone
3.0 gm. piperidine hydrochloride.
0.7 gm. paraformaldehyde
7.0 ml. alcohol (absolute)

The ketone and the piperidine hydrochloride are added to the alcohol in a 50 ml. conical flask fitted with a reflux condenser. The solids are dissolved by heating gently over a small bunsen flame. The para-:formaldehyde is added in small portions and the heating continued for 30 minutes. A clear light brown coloured liquid is obtained which on cooling and scratching crystallises to form a mass of pale yellow crystals. The solid is filtered off, washed with anhydrous ether and recrystallised from absolute alcohol to give white crystals, m.pt.135°-136°C. Yield 40%.

The hydrochloride is soluble in alchol and water but insoluble in ether.

	Found:	N,3.69%
Calculated for $C_{21}H_{31}O_3M$,HCl	:	N,3.67%

(b) Phenylhydrazone

4.0 gm. $C_{21}H_{31}O_3N$,HCl
1.25 gm. phenylhydrazine
20.0 ml. absolute alcohol
1.25 ml. acetic acid (glacial)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and acetic acid added. On cooling and scratching the phenyl-hydrazone crystallises out. The solid is filtered off, washed with a small amount of alcohol and recrystallised from alcohol to give yellow crystals, m.pt. 162°-163°C. Yield 74%.

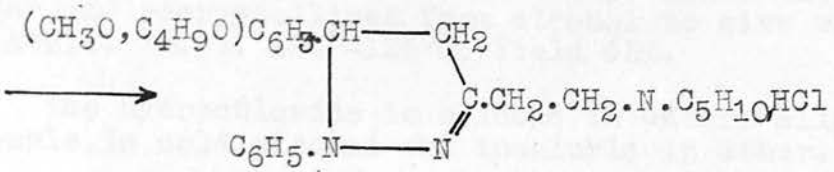
The /

The compound is slightly soluble in cold alcohol, fairly soluble in warm alcohol, insoluble in water and ether.

Found: N,9.1%
Calculated for $C_{27}H_{37}O_2N_3,HCl$ N,8.9%

(c) 1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline hydrochloride.

$(CH_3O,C_4H_9O)C_6H_3.CH:CH.C(=N.NH.C_6H_5).CH_2.CH_2.N.C_5H_{10},HCl$



2.0 gm. phenylhydrazone $C_{27}H_{37}O_2N_3,HCl$

20.0 ml. hydrochloric acid (N/1)

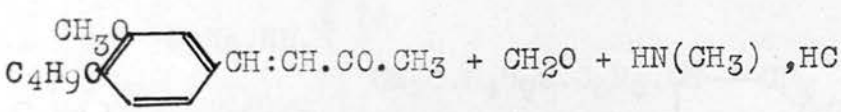
The phenylhydrazone is heated with the hydrochl-:oric acid in a small flask fitted with a reflux condenser. After refluxing for 30 minutes a clear green coloured solution is obtained which throws out a green coloured oil on cooling. Attempts to crystallise the oil at this stage are not successful. The aqueous layer is poured off and the oily residue dried in a vacuum over sulphuric acid and recrystallised from a small amount of absolute alcohol to give a white powder. m.pt. 188°-189°C. Yield 37%.

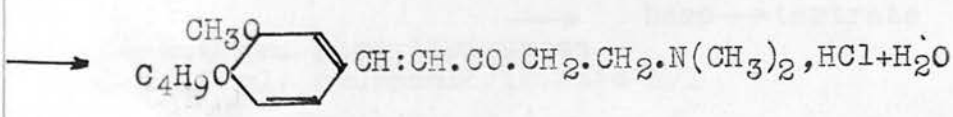
The compound is soluble in alcohol but only slightly soluble in water. A small portion placed on the tip of the tongue produces a distinct local anaesthetic action.

Found: N, 9.19%
Calculated for $C_{27}H_{37}O_2N_3,HCl$: N, 8.9%

1-Phenyl-5-(3'-methoxy-4'-n-butoxy)-3-β- dimethyl amino-ethyl-pyrazoline tartrate.

(a) 1-Dimethylamino-5-(3'-methoxy-4'-n-butoxyphenyl-Δ^4-penten-3-one hydrochloride.





10.0 gm. (1.0 mol.) n-butoxy-vanillidene acetone
2.0 gm. (1.7 mol.) paraformaldehyde
3.0 gm. (1.1 mol.) dimethylamine hydrochloride
10.0 ml. absolute alcohol

The n-butoxy-vanillidene acetone and the dimethylamine hydrochloride are dissolved in the alcohol by heating in a small flask fitted with a reflux condenser. The paraformaldehyde is divided into three portions and a third added to the flask at ten minute intervals while refluxing. A pale yellow solution is given which deposits crystals on cooling. The solid is filtered, washed with ether and recrystallised from alcohol to give white crystals. m.pt. 125°-126°C. Yield 55%.

The hydrochloride is soluble in water, slightly soluble in cold alcohol and insoluble in ether.

Found: N, 4.05 %
Calculated for $C_{18}H_{27}O_3N$,HCl : N, 4.10 %

(b) Phenylhydrazone.

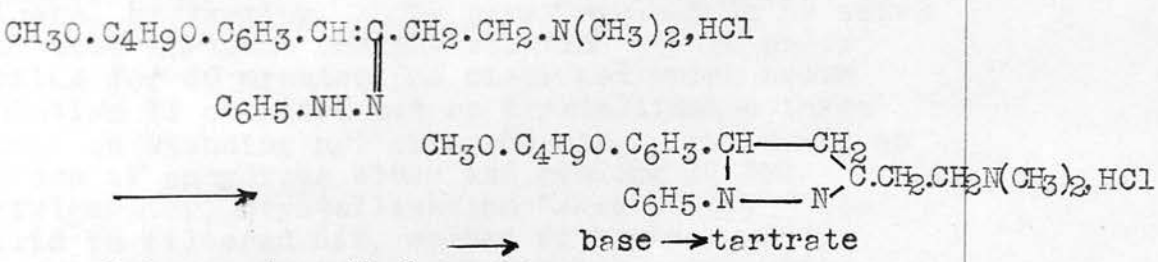
4.0 gm. $C_{18}H_{27}O_3N$,HCl
1.28 gm. phenylhydrazine
1.3 gm. acetic acid (glacial)
20.0 ml. absolute alcohol.

The unsaturated ketone is dissolved in the alcohol by warming and the phenylhydrazine and the acetic acid added. On cooling the phenylhydrazone crystallises out. The solid is filtered off, washed with a little alcohol and recrystallised from alcohol to give yellow crystals, m.pt. 143°-146°C. Yield 74%.

The compound is only slightly soluble in cold alcohol but more soluble in warm alcohol.

Found: N, 9.87%
$C_{24}H_{33}O_2N_3$,HCl required : N, 9.73%

(c) 1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate



2.0 gm. phenylhydrazone
20.0 ml. hydrochloric acid N/1

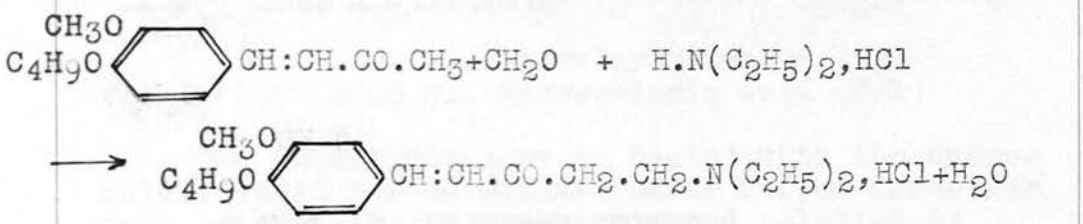
The /

The phenylhydrazone is heated with the hydrochloric acid under reflux on a water-bath for 30 minutes. The phenylhydrazone turns a bright orange colour and finally gives a greenish coloured solution which deposits a green coloured oily layer on cooling. The oily layer does not crystallise on standing nor on scratching. Water (20 ml.) is added and the solution washed with ethyl ether and the ether layer discarded. The aqueous solution is made slightly alkaline and the base extracted with ether. The ether solution is well washed with water, dried over anhydrous potassium carbonate, and the ether removed by heating on the water-bath. The base is finally dried in a vacuum desiccator to give a yellowish brown oil which does not crystallise. The base is taken up in absolute alcohol and the tartrate formed by adding the requisite amount of tartaric acid in alcohol. The tartrate is crystallised from petroleum ether and absolute alcohol to give a pale yellow powder. m.pt. 74°-76°C. Yield 37%.

Found : N, 8.2%
$C_{24}H_{33}O_2N_3, C_4H_6O_6$ requires : N, 8.06%

1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate.

(a) 1-Diethylamino-5-(3'-methoxy-4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



10.0 gm.	(1.0 mol.)	n-butoxy-vanillidene acetone
2.0 gm.	(1.7 mol.)	paraformaldehyde
4.95 gm.	(1.1 mol.)	diethylamine hydrochloride
10.0 ml.		alcohol (absolute)

The n-butoxy-vanillidene acetone and the diethylamine hydrochloride are dissolved in the alcohol by warming. The paraformaldehyde is added in three portions and the solution heated under reflux for 30 minutes. A clear yellowish brown solution is obtained but no crystallisation takes place on standing nor on scratching. By adding an excess of anhydrous ether and cooling in the refrigerator, crystallisation takes place. The solid is filtered off, washed with ether, and recrystallised from alcohol-ether to give white crystals. m.pt. 107°-109°C. Yield 23%.

The hydrochloride is soluble in water and in alcohol but insoluble in ether.

Found: N, 3.82%
$C_{20}H_{31}O_3N_1$,HCl requires : N, 3.79%

(b) /

(b) Phenylhydrazone

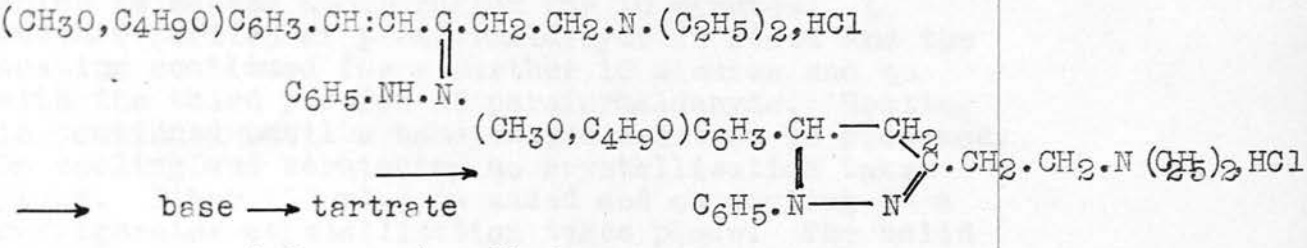
5.0 gm. $C_{20}H_{31}O_3N$,HCl
1.46 gm. phenylhydrazine
1.46 gm. acetic acid (glacial)
15.0 ml. alcohol (absolute)

The unsaturated ketone is dissolved in the alcohol and the acetic acid and the phenylhydrazine added. On standing the phenylhydrazone crystallises out. The solid is filtered off, washed with alcohol and recrystallised from alcohol to give yellow crystals, m.pt. 132°-135°C. Yield 68%.

The compound is only slightly soluble in cold alcohol but more soluble in warm alcohol.

Found: N, 9.02%
$C_{26}H_{37}O_2N_3$,HCl required: N, 9.14%

(c) 1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate.



3.0 gm. phenylhydrazone
30.0 ml. hydrochloric acid (N/1)

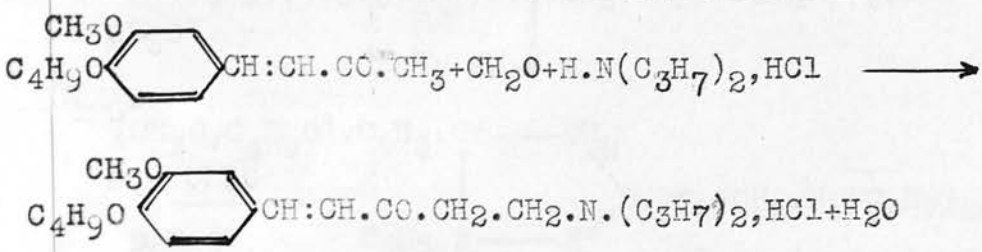
The phenylhydrazone is heated with the hydrochloric acid for 30 minutes under reflux condenser on a water-bath. A green coloured solution is obtained which deposits a green coloured oil on cooling. The oily layer does not crystallise on standing nor after repeated attempts to induce crystallisation by scratching or seeding. Water (20 ml.) is added to bring the hydrochloride into solution and the base liberated by making slightly alkaline with sodium hydroxide solution. The liberated base is taken up in ether, the ether solution well washed with water, dried over anhydrous potassium carbonate, and the ether removed on the steam-bath. The base is dried in a vacuum desiccator and the equivalent amount of tartaric acid in alcoholic solution is added, and the tartrate recrystallised from alcohol-petroleum ether to give pale yellow powder, m.pt. 54°-56°C. Yield 47%.

The compound is soluble in water, very soluble in alcohol but insoluble in ether.

Found: N, 7.25%
$C_{26}H_{37}O_2N_3$,$C_4H_6O_6$ requires : N, 7.33%

1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3- β-di-n-propylamino-ethyl-pyrazoline tartrate.

(a) 1-Di-n-propylamino-5-(3'-methoxy-4'-n-butoxy-phenyl)- Δ 4-penten-3-one-hydrochloride.



10.0 gm. (1.0 mol.) n-butoxy-vanillidene acetone
2.06 gm. (1.7 mol.) paraformaldehyde
5.52 gm. (1.1 mol.) di-n-propylamine hydrochloride
15.0 ml. alcohol (absolute)

The n-butoxy-vanillidene acetone and the di-n-propylamine hydrochloride are dissolved in the alcohol by warming. The paraformaldehyde is divided into three portions and a third added to the solution which is heated under reflux for 10 minutes. A further portion of paraformaldehyde is added and the heating continued for a further 10 minutes and so with the third portion of paraformaldehyde. Heating is continued until a homogeneous solution is produced. On cooling and scratching no crystallisation takes place. Ether (10 ml.) is added and on cooling in a refrigerator crystallisation takes place. The solid is filtered off, washed with anhydrous ether and recrystallised from alcohol-ether to give white crystals, m.pt. 120°- 121°C. Yield 42%.

The compound is soluble in water, soluble in alcohol, but insoluble in ether.

Found: N, 3.6%
$C_{22}H_{35}O_3N$,HCl requires : N, 3.52%

(b) Phenylhydrazone

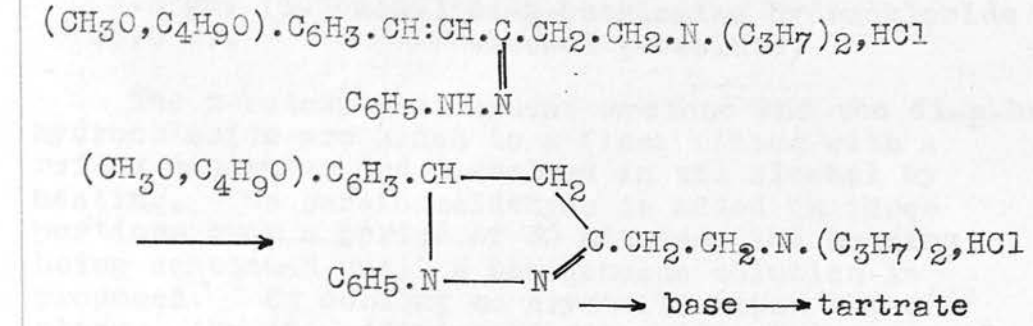
5.0 gm. $C_{22}H_{35}O_3N$,HCl
1.36 gm. phenylhydrazine
1.4 gm. acetic acid (glacial)
15.0 ml. alcohol (absolute)

The unsaturated ketone is dissolved in the alcohol with the aid of heat and the phenylhydrazine and acetic acid added. On cooling and scratching crystallisation takes place. The solid is filtered off, washed with alcohol and recrystallised from alcohol to give yellow crystals, m.pt. 149°- 150°C. Yield 64%.

The compound is slightly soluble in cold alcohol but more soluble in warm alcohol. It is insoluble in water.

Found: N, 8.7%
$C_{28}H_{41}O_2N$,HCl requires : N, 8.62%

(c) 1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3- β-di-n-propylamino-ethyl-pyrazoline tartrate.



3.0 gm. phenylhydrazone
30.0 ml. hydrochloric acid (N/1)

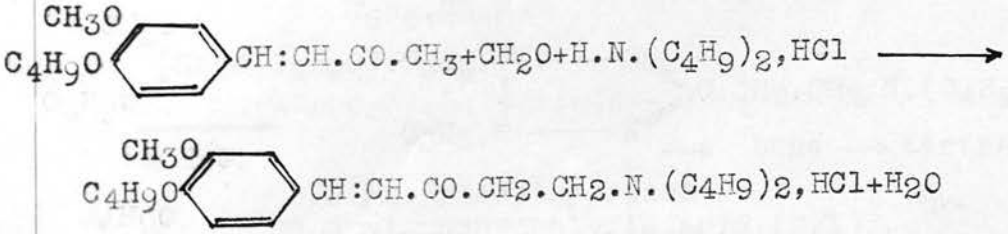
The phenylhydrazone is heated on a steam-bath under reflux with the hydrochloric acid for 30 minutes. The rate of conversion to the pyrazoline is slower than in the previous reactions. A green coloured solution is obtained which deposits a greenish oil on cooling. The oily layer does not crystallise on scratching or seeding. Water (20 ml.) is added and the aqueous solution washed with ether and the ether layer discarded. The solution is made faintly alkaline by the addition of sodium hydroxide and the liberated base extracted with ether. The ether solution is washed with water, dried over anhydrous potassium carbonate and the ether removed on the steam-bath. The base is obtained as a pale yellow oil which does not crystallise. The tartrate is obtained by the addition of tartaric acid in alcohol, and recrystallised from alcohol-petroleum-ether to give a pale yellow powder, m.pt. 68°-69°C. Yield 35%.

The tartrate is soluble in water and very soluble in alcohol. It gives a distinct local anaesthetic action when applied to the tip of the tongue.

Found: N, 6.8%
$C_{23}H_{41}O_2N_3,C_4H_6O_6$ requires: N, 6.98%

1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3- β-di-n-butylamino-ethyl-pyrazoline tartrate.

(a) 1-Di-n-butylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)- Δ^4-penten-3-one-hydrochloride.



10.0 gm. (1.0 mol.) n-butoxy-vanillidene acetone
2.11 gm. (1.1 mol.) paraformaldehyde
7.3 gm. (1.7 mol.) di-n-butylamine hydrochloride
15.0 ml. alcohol (absolute)

The n-butoxy-vanillidene acetone and the di-n-butylamine hydrochloride are added to a flask fitted with a reflux condenser and dissolved in the alcohol by heating. The paraformaldehyde is added in three portions over a period of 30 minutes, the heating being continued until a homogeneous solution is produced. On cooling no crystallisation takes place. On the addition of ether (20 ml.) and cooling for several days in a refrigerator crystallisation takes place. The compound is crystallised from acetone-ether to give white crystals, m.pt.122°-123°C. Yield 43%.

The compound is fairly soluble in water, very soluble in alcohol but insoluble in ether.

Found: N, 3.5%
$C_{24}H_{39}O_3N,HCl$ requires : N, 3.29%

(b) Phenylhydrazone.

7.0 gm. $C_{24}H_{39}O_3N,HCl$
1.78 gm. phenylhydrazine
1.78 gm. acetic acid (glacial)
20.0 ml. alcohol (absolute)

The unsaturated ketone is dissolved in the alcohol by warming and the phenylhydrazine and the acetic acid added. After cooling and seeding the phenylhydrazone crystallises out and is recrystallised from alcohol to give yellow crystals, m.pt. 135°-136°C. Yield 72%.

The compound is insoluble in water but soluble in alcohol.

Found: N, 8.3%
$C_{30}H_{45}O_2N,HCl$ requires : N, 8.15%

(c) 1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate.

$(CH_3O,C_4H_9O).C_6H_3.CH{:}CH.C(=N.NH.C_6H_5).CH_2.CH_2.N.(C_4H_9)_2,HCl$

$(CH_3O,C_4H_9O).C_6H_5.CH(-N(C_6H_5)-N=C).CH_2.CH_2.N.(C_4H_9)_2,HCl$ → base → tartrate

3.0 gm. phenylhydrazone
30.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

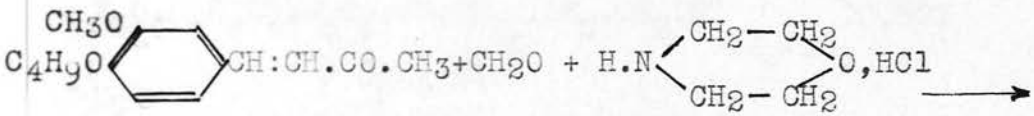
The phenylhydrazone is heated with the hydrochloric acid and the alcohol in a flask fitted with a reflux condenser. The heating is continued for 40 minutes. A greenish brown solution is obtained which deposits a greenish oil on cooling but this does not crystallise. Water (20 ml.) is added and the solution washed with ether and the ether layer discarded. The aqueous layer is made slightly alkaline with sodium hydroxide and the base extracted with ether. The ether solution is washed with water and dried over anhydrous potassium carbonate and the ether removed on the steam-bath. The free base is dried in a vacuum desiccator over sulphuric acid. The base is a yellow coloured oil which does not crystallise. The tartrate is formed by the addition of tartaric acid in alcohol and the tartrate recrystallised from alcohol-petroleum-ether to form a yellow micro-crystalline powder, m.pt. 89°-90°C. Yield 30%.

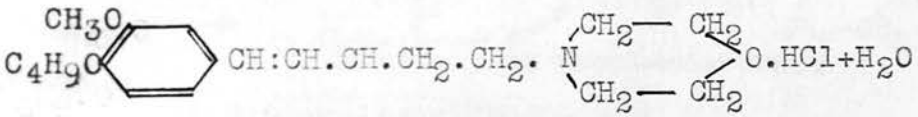
Found: N, 6.62%
$C_{30}H_{45}O_2N_3, C_4H_6O_6$ requires: N, 6.57%

The compound is fairly soluble in water, very soluble in alcohol, but insoluble in ether. When a small portion is placed on the tongue it produces a local anaesthetic action.

1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-morpholino-ethyl-pyrazoline tartrate.

(a) 1-Morpholino-5-(3'-methoxy-4'-n-butoxy-phenyl)-Δ^4-penten-3-one-hydrochloride.





10.0 gm. (1.0 mol.) n-butoxy-vanillidene acetone
2.0 gm. (1.7 mol.) paraformaldehyde
5.4 gm. (1.1 mol.) morpholine hydrochloride
15.0 ml. (1.1 mol.) alcohol (absolute)

The n-butoxy-vanillidene acetone and the morpholine hydrochloride are dissolved by heating with the alcohol in a small flask fitted with a reflux condenser. The paraformaldehyde is added in three portions over a period of half an hour. A clear yellowish solution is formed which rapidly crystallises on cooling to form a mass of light brown crystals. The solid is filtered off, washed with ether and recrystallised from alcohol to give white crystals, m.pt. 154°-155°C. Yield 65%.

The compound is only slightly soluble in water, but more soluble in warm alcohol. It is insoluble in ether.

Found: N, 3.60%
$C_{20}H_{29}O_4N$,HCl requires : N, 3.65%

(b) Phenylhydrazone of 1-morpholino-5-(3'-methoxy-4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

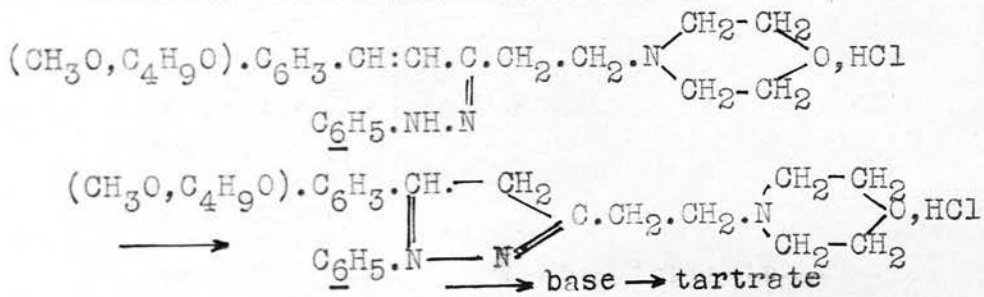
4.0 gm. $C_{20}H_{29}O_4N$,HCl
1.18 gm. phenylhydrazine
1.4 gm. acetic acid (glacial)
15.0 ml. alcohol (absolute)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and acetic acid added. On cooling and scratching crystallisation takes place rapidly. The phenylhydrazone is filtered off, washed with alcohol, and recrystallised from alcohol to give yellow crystals, m.pt. 152°-153°C. Yield 86%.

The compound is only slightly soluble in cold alcohol and not much more soluble in warm alcohol. It is insoluble in water.

Found: N, 8.61%
$C_{26}H_{35}O_3N_3$,HCl requires: N, 8.87%

(c) 1-Phenyl-5-(3'-methoxy-4'-n-butoxy-phenyl)-3-β-morpholino-ethyl-pyrazoline tartrate.



2.0 gm. phenylhydrazone
20.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol.

The phenylhydrazone is heated with the alcohol and hydrochloric acid in a small flask fitted with a reflux condenser. Heating without the addition of the alcohol does not bring about the isomeric change to the pyrazolime probably due to the insolubiluty of the phenylhydrazone. On the addition of the alcohol the isomeric change takes place; a reddish colour is first produced followed by the greenish solution characteristic of the pyrazolines. Heating on the steam-bath is continued for 30 minutes to complete the reaction. After cooling water (20 ml.) is added /

added and the solution is washed with ether and the ether layer discarded. The aqueous layer is made alkaline with sodium hydroxide and the base extracted with ether. The ether solution is washed with water and dried over anhydrous potassium carbonate and the ether removed on the steam-bath. The base is obtained as a yellow oil which does not crystallise. The requisite amount of tartaric acid in alcohol is added and the tartrate recrystallised from alcohol-petroleum-ether to give a yellow crystal, m.pt. 40°- 42°C. Yield 46%.

The compound is soluble in water and soluble in alcohol. It has a slight local anaesthetic action when a small portion is placed on the tip of the tongue.

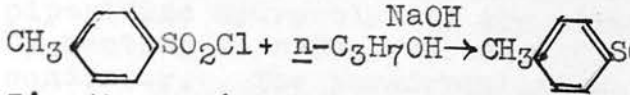
Found: N, 7.2%

$C_{26}H_{35}O_3N_3, C_4H_6O_6$ requires: N, 7.15%

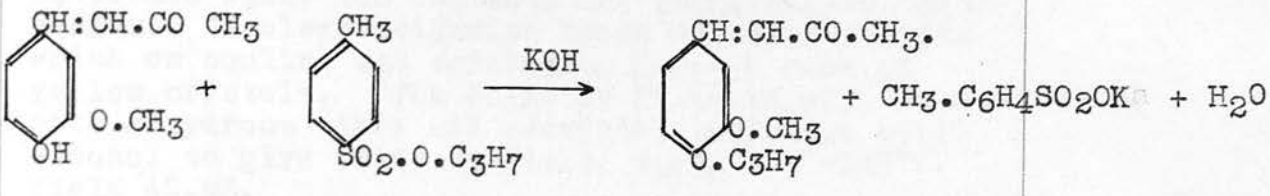
(2) β-Amino-ketones and related pyrazolines derived from 3'-methoxy-4'-n-propoxy-benzylidene-acetone.

n-Propyl-p-toluenesulphonate

(Organic Syn., Vol. IX., 29)



3'methoxy-4'-n-propoxy-benzylidene acetone



192 gm.	(1.1 mol.)	vanillidene acetone
107 gm.	(1.0 mol.)	n-propyl-p-toluenesulphonate
35 gm.		potassium hydroxide
250 ml.		ethyl alcohol 95%

The vanillidene acetone is dissolved in the alcohol by heating in a flask fitted with a reflux condenser. The n-propyl-p-toluene-sulphonate is added to the solution followed by the potassium hydroxide dissolved in the minimum of water. The flask is heated under reflux for one and a half hours and then the contents are cooled and poured into 2½ litres of water. The 3'-methoxy-4'-n-propoxy-benzylidene-acetone is thrown out of solution as a yellow oil which crystallises on standing. The solid is filtered off, washed with water, dried and recrystallised from alcohol to give yellow crystals, m.pt. 92° - 93 C°. Yield 80%.

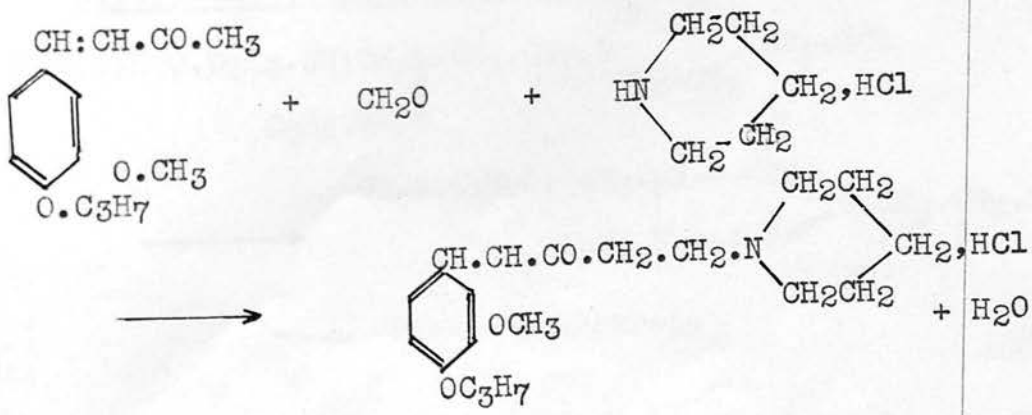
The compound is insoluble in water and slightly soluble in alcohol.

Found: C, 71.2%; H, 7.59%

$C_{14}H_{18}O_3$ requires : C, 71.8%; H, 7.69%

1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-piperidino-ethyl pyrazoline tartrate.

(a) 1-Piperidino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-3-one hydrochloride.



10.0 gm.	(1.0 mol.)	3'-methoxy-4'-n-propoxy-benzylidene-acetone
3.65gm.	(1.0 mol.)	piperidine hydrochloride
2.18gm.	(1.7 mol.)	paraformaldehyde
10.0 ml.		ethyl alcohol (absolute)

The alkoxy-benzylidene-acetone and the piperidine hydrochloride are dissolved in the alcohol by heating in a small flask fitted with a reflux condenser. The paraformaldehyde is divided into three portions and added to the flask at 10 minute intervals while the contents are being heated under reflux. A clear yellowish brown solution results which on cooling and scratching forms a mass of yellow crystals. The solid is filtered off, washed with anhydrous ether and recrystallised from ethyl alcohol to give white crystals, m.pt. 146°-147°C. Yield 45.6%.

The compound is soluble in water and readily soluble in alcohol.

Found: N, 4.2%.

$C_{20}H_{29}O_3N,HCl$, requires: N, 3.8%.

(b) Phenylhydrazone of 1-piperidino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

6.0	gm.	$C_{20}H_{29}O_3N,HCl$
1.77	gm.	phenylhydrazine
1.77	gm.	acetic acid (glacial)
15.0	ml.	ethyl alcohol (absolute)

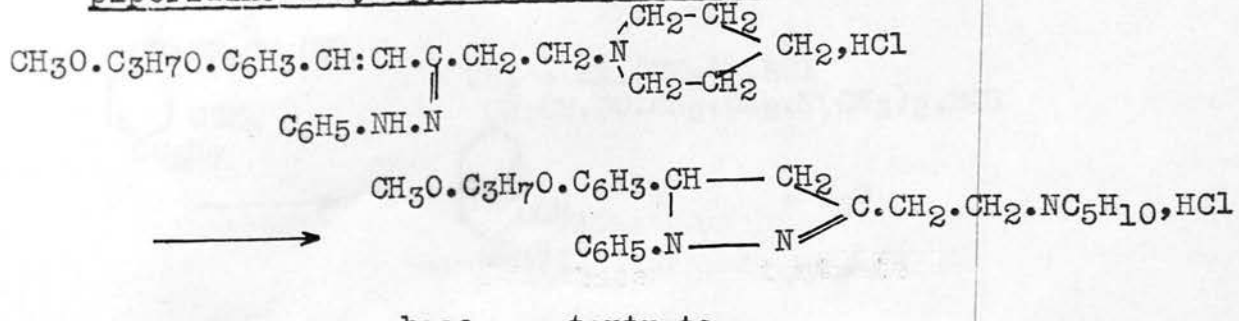
The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling and scratching, crystallisation takes place. The solid is filtered, washed with alcohol and recrystallised from alcohol to give yellow crystals, m.pt. 168° - 169°C. Yield 64%.

The compound is only slightly soluble in cold alcohol and not very soluble in warm alcohol. It is insoluble in water.

Found: N, 8.91%

$C_{26}H_{35}O_2N_3HCl$ requires : N, 9.18%.

(c) 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate.



3.0 gm. phenylhydrazone
30.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol for thirty minutes. The pyrazoline hydrochloride is formed as a green coloured solution and is deposited as a green viscous oil on cooling. The hydrochloride is re-dissolved by the addition of water (20 ml.) and the base liberated by sodium hydroxide. The base is extracted with ether, the ether solution washed with water, dried over anhydrous potassium carbonate and the ether removed on the steam-bath. The tartrate is formed by the addition to the base of tartaric acid in alcohol and is recrystallised from acetone to give pale yellow crystals, m.pt. 66° - 68°C. Yield 42%.

The compound is soluble in water, very soluble in alcohol and gives a local anaesthetic action when a small portion is placed on the tip of the tongue.

Found: N, 7.2 %.
$C_{26}H_{35}O_2N_3, C_4H_6O_6$ requires: N, 7.35%.

1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-piperidino-ethyl picrate.

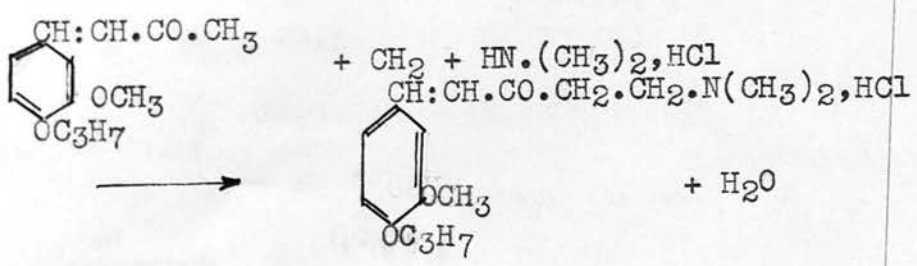
The base is dissolved in alcohol and the equivalent amount of picric acid in alcoholic solution added. The picrate crystallises on standing and is recrystallised from alcohol to give light brown crystals, m.pt. 143° - 144°C.

The picrate is insoluble in water and when a small portion is placed on the tip of the tongue it fails to produce local anaesthesia.

Found: N, 12.3%.
$C_{26}H_{35}O_2N_3, C_6H_2(NO_2)_3.OH$ requires: N, 12.7%.

1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate.

(a) 1-Dimethylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



10.0 gm.	(1.0 mol.)	3'-methoxy-4'-n-propoxy-benzylidene acetone
2.18 gm.	(1.7 mol.)	paraformaldehyde
3.25 gm.	(1.1 mol.)	dimethylamine hydrochloride
10.0 ml.		ethyl alcohol (absolute)

The alkoxy-benzylidene-acetone and the dimethylamine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and added to the flask at intervals over thirty minutes while refluxing. A yellowish brown solution is obtained which deposits crystals on cooling. The solid is filtered, washed with anhydrous ether and recrystallised from alcohol to give white crystals, m.p. 133° - 134°C. Yield 51%.

The hydrochloride is soluble in water and in alcohol but insoluble in ether.

	Found:	N, 4.1%
$C_{17}H_{25}O_3N,HCl$	requires:	N, 4.3%.

(b) Phenylhydrazone of 1-dimethylamino-5-(3-methoxy-4-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

4.0 gm.	$C_{17}H_{25}O_3N,HCl$
1.25 gm.	phenyldydrazine
1.3 gm.	acetic acid (glacial)
30.0 ml.	ethyl alcohol (absolute)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling and scratching crystallisation takes place. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.p. 164°-165°C. Yield 70%.

The compound is only slightly soluble in cold alcohol and not very soluble in warm alcohol. It is insoluble in water.

	Found:	N, 10.1%
$C_{23}H_{31}O_3N_3HCl$	requires:	N, 9.8%.

(c) 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate.

$$CH_3.C_3H_7O.C_6H_3.CH{:}CH.C(=N.NH.C_6H_5).CH_2.CH_2.N(CH_3)_2,HCl$$

$$\longrightarrow CH_3O.C_3H_7O.C_6H_3.CH(-N(C_6H_5)-N=C.CH_2.CH_2.N(CH_3)_2,HCl)-CH_2$$

$\longrightarrow$ base $\longrightarrow$ tartrate

2.5 gm. phenylhydrazone
25.0 ml. hydrochloric acid (N/1)

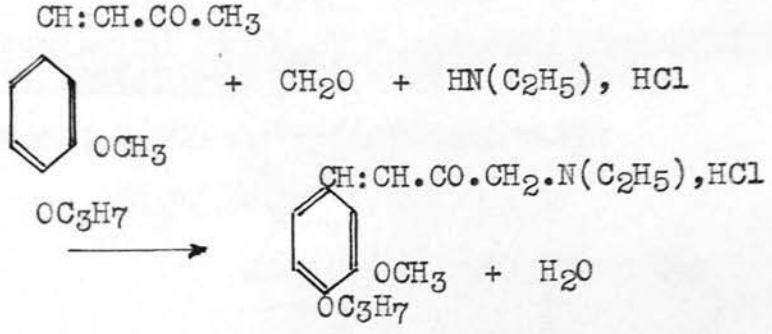
The phenylhydrazone is heated under reflux with the hydrochloric acid for thirty minutes. The pyrazoline hydrochloride is formed as a green coloured solution and is deposited as a green viscous oil on cooling. The hydrochloride is redissolved by the addition of water (30 ml.) and the base liberated with sodium hydroxide. The base is taken up in ether, the ether solution washed with water, dried and the ether removed on the steam-bath. The tartrate is formed by adding to the base the equivalent amount of tartaric acid dissolved in alcohol and recrystallising from alcohol-petrol-ether to give pale yellow crystals, m.pt. 79° - 80°C. Yield 44%.

The compound is soluble in water and very soluble in alcohol. A small portion placed on the tip of the tongue produces local anaesthesia.

Found: N, 7.5 %
$C_{23}H_{31}N_3O_2, C_4H_6O_6$ requires: N, 7.68%.

1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate.

(a) 1-Diethylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



10.0 gm. (1.0 mol.) 3-methoxy-4-n-propoxy-benzylidene-acetone
2.18 gm. (1.7 mol.) paraformaldehyde
5.1 gm. (1.1 mol.) diethylamine hydrochloride
10.0 ml. ethyl alcohol (absolute)

The alkoxy-benzylidene-acetone and the diethylamine hydrochloride are dissolved in the alcohol by heating in a small flask fitted with a reflux condenser. The paraformaldehyde is divided into three portions and added to the flask over a period of 30 minutes while refluxing. A clear light brown solution is obtained which on cooling and scratching deposits a small amount of crystals. By adding

10/

10 ml. anhydrous ether and cooling in a refrigerator further crystallisation takes place. The solid is filtered, washed with ether and recrystallised from an alcohol-ether to give white crystals, m.pt. 103° - 104°C. Yield 43%.

The compound is soluble in water and in alcohol but insoluble in ether.

Found: N, 3.5%
$C_{19}H_{29}O_3N$,HCl requires: N, 3.9%.

(b) Phenylhydrazone of 1-diethylamino -5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ4-penten-3-one hydrochloride.

4.0 gm. $C_{19}H_{29}O_3N$,HCl
1.22 gm. phenylhydrazine
1.22 gm. acetic acid (glacial)
12.0 ml. ethyl alcohol (absolute)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On standing the phenylhydrazone crystallises out. The solid is filtered, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 143° - 144°C. Yield 72%.

The compound is fairly soluble in warm alcohol but insoluble in water.

Found: N, 9,42%
$C_{25}H_{35}O_2N$,HCl requires: N, 9.41%

(c) 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate.

$CH_3O.C_3H_7O.C_6H_3.CH{:}C.CH_2CH_2.N(C_2H_5)_2$,HCl

$C_6H_5.NH.N$

$CH_3O.C_3H_7O.C_6H_3.CH$ — CH_2
$C.CH_2.CH_2.N(C_2H_5)_2$,HCl
$C_6H_5.N$ — N

→ base → tartrate

2.5 gm. $C_{25}H_{35}O_2N_3$,HCl
25.0 ml. hydrochloric acid (N/1)

The phenylhydrazone is heated under reflux with the hydrochloric acid for thirty minutes. The pyrazoline hydrochloride is formed as a green coloured solution and is deposited as a green viscous oil on cooling. The hydrochloride is redissolved by the addition of water (20 ml.) and the base liberated by adding sodium hydroxide. The base/

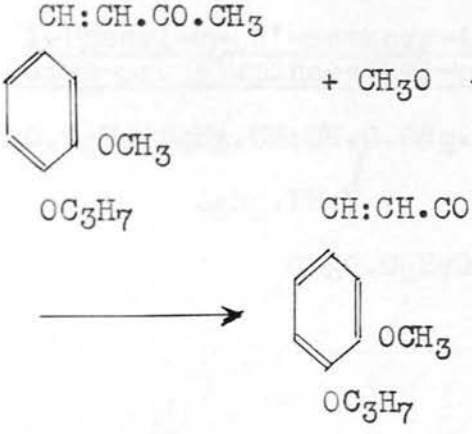
base is taken up in ether, the ether solution washed with water, dried and the ether removed on the steam-bath. The tartrate is formed by the addition to the base of the equivalent amount of tartaric acid dissolved in alcohol and recrystallising from acetone to give yellow crystals, m.pt. 46° - 48°C. Yield 38%.

The compound is soluble in water and alcohol. It produces a strong local anaesthetic action when a small portion is placed on the tip of the tongue.

Found: N, 7.3%
$C_{25}H_{35}O_2N_3,C_4H_6O_6$ requires: N, 7.5%.

1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate.

(a) 1-Dipropylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



10.0 gm.(1.0 mol.) 3'-methoxy-4'-n-propoxy-benzylidene acetone
2.18 gm.(1.7 mol.) paraformaldehyde
6.45 gm.(1.1 mol.) di-n-propylamine hydrochloride
10.0 ml. ethyl alcohol (absolute).

The alkoxy-benzylidene acetone and the di-n-propylamine hydrochloride are dissolved in the alcohol by heating in a flask fitted with a reflux condenser. The paraformaldehyde is divided into three portions and added to the flask at 10 minute intervals during the refluxing which is continued for 30 minutes. A clear solution is obtained which only partly crystallises on standing. On the addition of 10 ml. anhydrous ether and cooling in a refrigerator a better yield is obtained. The solid is filtered, washed with ether and recrystallised from alcohol-ether to give white crystals, m.pt. 124° - 125°C. Yield 46%.

The compound is soluble in water and very soluble in alcohol but practically insoluble in ether.

Found/

Found: N, 3.48%
$C_{21}H_{33}O_3N$,HCl requires: N, 3.65%.

(b) Phenylhydrazone of 1-di-n-propylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

6.0 gm. $C_{21}H_{33}O_3N$,HCl
1.63 gm. phenylhydrazine
1.6 gm. acetic acid (glacial)
15.0 ml. ethyl alcohol (95%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and acetic acid added. On standing the phenylhydrazone crystallises. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 154° - 155°C. Yield 84%.

Found: N, 9.02%
$C_{27}H_{39}O_2N_3$,HCl requires: N, 8.87%.

(c) 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate.

$CH_3O.C_3H_7.C_6H_3.CH:CH.C.CH_2.CH_2.N(C_3H_7)_2$,HCl
$C_6H_5.NH.N$

$CH_3O.C_3H_7O.C_6H_3.CH.$ — CH_2
$C.CH_2.CH_2.N(C_3H_7)_2$,HCl
$C_6H_5.N$ — N

→ base → tartrate

2.5 gm. $C_{27}H_{39}O_2N_3$,HCl
25.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol, and a green coloured solution of the pyrazoline hydrochloride is formed. The base is liberated by the addition of sodium hydroxide and is taken up in ether. The ether solution is washed with water, dried and the ether removed on the steam-bath. The tartrate is formed by the addition to the base of the equivalent amount of tartaric acid in alcohol and is recrystallised from acetone to give pale yellow crystals, m.pt. 54° - 55°C. Yield 28%

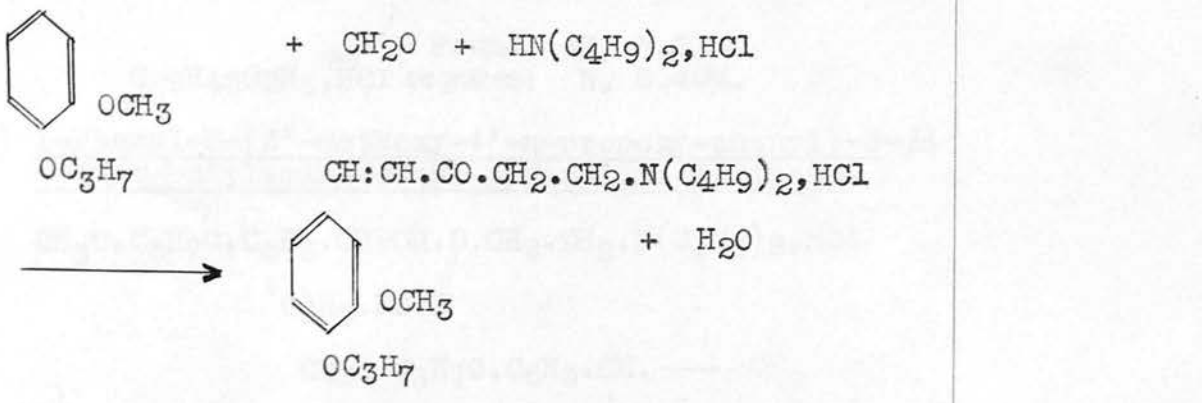
The compound is soluble in water and very soluble in alcohol. It produces local anaesthesia when a small portion is placed on the tip of the tongue.

Found/

Found: N, 7.3 %
$C_{27}H_{39}O_2N_3,C_4H_6O_6$ requires: N, 7.13%.

1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate.

(a) 1-Di-n-butylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



10.0 gm. (1.0 mol.) 3-methoxy-4-n-propoxy-benzylidene-acetone
2.18 gm. (1.7 mol.) paraformaldehyde
7.75 gm. (1.1 mol.) di-n-butylamine hydrochloride
15.0 ml. ethyl alcohol (absolute).

The alkoxy benzylidene acetone and the di-n-butylamine hydrochloride are dissolved in the alcohol by heating in a flask fitted with a reflux condenser. The paraformaldehyde is divided into three portions and added to the flask at 10 minute intervals during refluxing which is continued for 30 minutes. A clear solution is obtained which on cooling and scratching forms a mass of light brown crystals. The solid is transferred to a filter, washed with anhydrous ether and recrystallised from acetone-ether to give white crystals, m.pt. 93° - 95°C. Yield 43%.

The hydrochloride is soluble in water and in alcohol but insoluble in ether.

Found: N, 3.42%
$C_{23}H_{37}O_3N,HCl$ requires: N, 3.40%.

(b) Phenylhydrazone of 1-n-dibutylamino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

6.0 gm. $C_{23}H_{37}O_3N,HCl$
1.10 gm. phenylhydrazine
1.10 gm. acetic acid (glacial)
10.0 ml. ethyl alcohol (95%)

The/

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. Crystallisation takes place slowly. The phenylhydrazone is transferred to a filter, washed with a little alcohol and recrystallised from alcohol to give yellow needles, m.pt. 143° - 144°C. Yield 74%.

The compound is not very soluble in alcohol even on warming. It is insoluble in water.

Found: N, 8.81%
$C_{29}H_{43}O_2N_3$,HCl requires: N, 8.40%.

(c) 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate.

$CH_3O.C_3H_7O.C_6H_3.CH:CH.C.CH_2.CH_2.N(C_4H_9)_2$,HCl
$C_6H_5.NH.N$

$CH_3O.C_3H_7O.C_6H_3.CH.$ —— CH_2
$C.CH_2.CH_2.N(C_4H_9)_2$,HCl
$C_6H_5.N$ —— N

→ base → tartrate

2.0 gm. $C_{29}H_{43}O_2N_3$,HCl
20.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol and a green coloured solution of the pyrazoline hydrochloride is formed. Water (20 ml.) is added and the base liberated by adding sodium hydroxide. The base is taken up in ether, washed with water, dried and the ether removed on the steam-bath. The tartrate is formed by adding to the base the equivalent of tartaric acid in alcohol and recrystallising from acetone to give yellow crystals, m.pt. 54° - 55°C. Yield 28%.

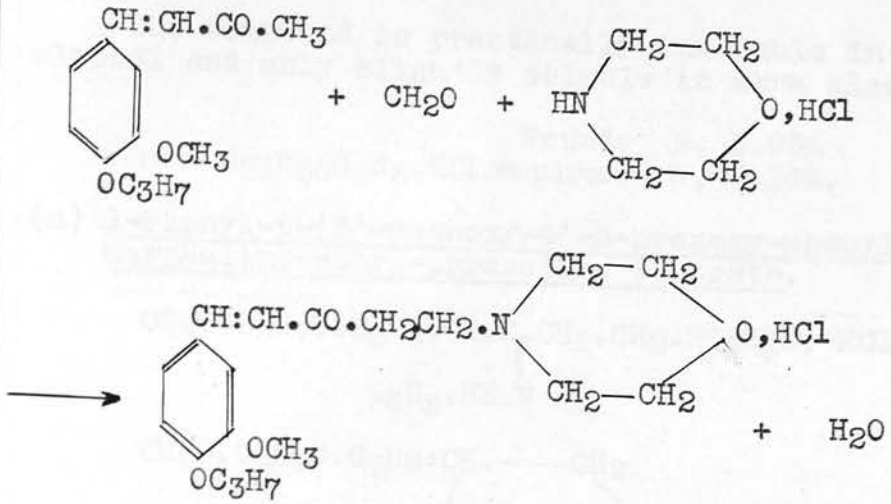
? meaning

The compound is soluble in water and in alcohol but insoluble in ether. A small portion placed on the tip of the tongue produces local anaesthesia.

Found: N, 7.04%
$C_{29}H_{43}O_2N_3,C_4H_6O_6$ requires: N, 6.83%.

1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-morpholino-ethyl-pyrazoline tartrate.

(a) 1-Morpholino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



7.0 gm. (1.0 mol.) 3'-methoxy-4'-n-propoxy-benzylidene-acetone

1.5 gm. (1.7 mol.) paraformaldehyde
4.0 gm. (1.1 mol.) morpholine hydrochloride
15.0 ml. ethyl alcohol (absolute).

The alkoxy-benzylidene-acetone and the morpholine hydrochloride are dissolved in the alcohol by heating in a flask fitted with a reflux condenser. The paraformaldehyde is divided into three portions and a third portion added to the flask at 10 minute intervals while heating under reflux. A clear solution is produced which crystallises rapidly on cooling to form a mass of light brown crystals. The solid is transferred to a filter, washed with a little alcohol and recrystallised from alcohol to give white crystals, m.pt. 164° - 165°C. Yield 55%.

The compound is slightly soluble in water and only slightly soluble in warm alcohol.

	Found:	N, 3.8 %
$C_{19}H_{27}O_3N,HCl$	requires:	N, 4.08%.

(b) Phenylhydrazone of 1-morpholino-5-(3'-methoxy-4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

5.0 gm. $C_{19}H_{27}O_3N,HCl$
1.4 gm. phenylhydrazine
1.4 gm. acetic acid (glacial)
20.0 ml. ethyl alcohol (90%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling crystallisation takes place rapidly. The phenylhydrazone is filtered, washed with a little alcohol and recrystallised from alcohol to give yellow needles, m.pt. 158° - 159°C. Yield 85%.

The compound is practically insoluble in cold alcohol and only slightly soluble in warm alcohol.

Found: N, 8.95%
$C_{25}H_{33}O_3N_3$,HCl requires: N, 9.14%.

(c) 1-Phenyl-5-(3'-methoxy-4'-n-propoxy-phenyl)-3-β-morpholino-ethyl-pyrazoline tartrate.

$CH_3O.C_3H_7O.C_6H_3.CH.C.CH_2.CH_2.NC_4H_8O$, HCl

$C_6H_5.NH.N$

$CH_3O.C_3H_7O.C_6H_3.CH.——CH_2$

$C.CH_2.CH_2.NC_4H_8O$,HCl

$C_6H_5.N——N$

→ base → tartrate

4.0 gm. phenylhydrazone
40.0 ml. hydrochloric acid (N/1).
10.1 ml. ethyl alcohol

The phenylhydrazone is heated with the hydrochloric acid and the alcohol under reflux for 30 minutes. A greenish coloured solution is produced which deposits a green coloured oil on cooling. Water (30 ml.) is added and the solution is made slightly alkaline with sodium hydroxide solution. The base which separates is extracted with ether, the ether solution washed with water, dried over anhydrous potassium carbonate and the ether removed on the steam-bath. The tartrate is formed by the addition of tartaric acid in alcohol to the base and recrystallised from alcohol-petroleum-ether to give pale yellow crystals, m.pt. 64° - 65°C. Yield 32%.

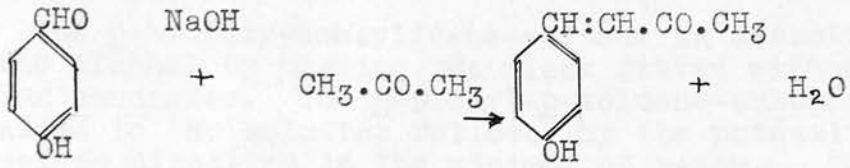
The compound is slightly soluble in water and more soluble in alcohol. It produces a slight local anaesthetic action when a small portion is placed on the tip of the tongue.

Found: N, 8.52%
$C_{25}H_{33}O_3N_3,C_2H_3O_3$ requires: N, 8.43%.

$\frac{1}{2}\ C_4H_6O_6$.

(3) β-Amino-ketones and related pyrazolines derived from 4-n-propoxy-benzylidene acetone

p-Hydroxy-benzylidene-acetone



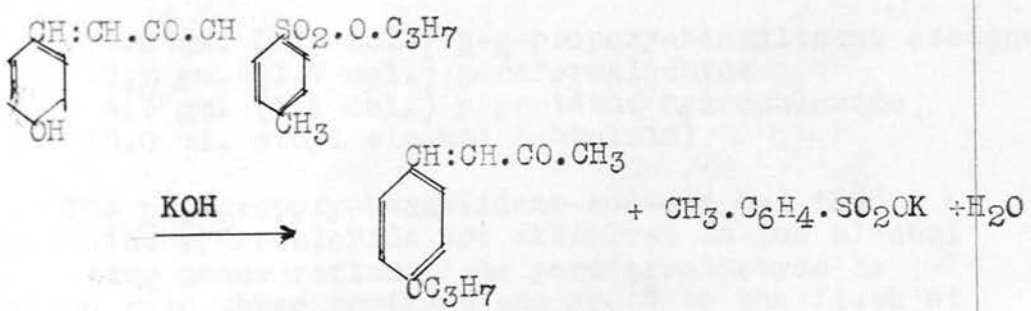
100 gm. p-hydroxy-benzaldehyde
420 ml. acetone
130 ml. sodium hydroxide solution (50%)
250 ml. water

The p-hydroxy-benzaldehyde is dissolved in the acetone and while the solution is being constantly agitated the sodium hydroxide solution is slowly added. A slight precipitate is formed but this is brought into solution by adding the water and heating on the steam-bath under reflux for about 10 minutes. On cooling the solution throws out an oily layer which crystallises after standing at room temperature for 48 hours. Acetic acid is added until the solution is faintly acid. [illegible] and the excess acetone is removed by distilling on the steam-bath. On cooling, the liquid forms a mass of reddish brown crystals. The solid is transferred to a filter, washed with water, and recrystallised from alcohol (95%) to form pale yellow crystals, m.pt. 104°- 105°C. Yield 60%

The compound is readily soluble in alcohol and in acetone but insoluble in water.

Found C,74.32;H,6.51%
$C_{10}H_{10}O$ requires: C,74.1; H,6.17%

p-n-propoxy-benzylidene-acetone



81 gm. p-hydroxy-benzylidene-acetone
107 gm. n-propyl-p-toluene-sulphonate
70 gm. potassium hydroxide
250 ml. ethyl alcohol (95%)
2500 ml. water

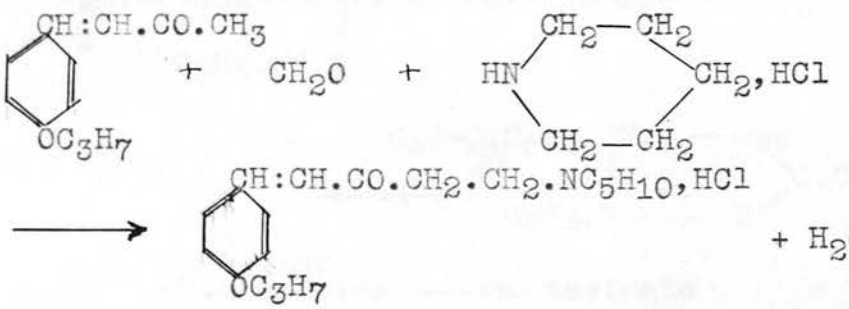
The p-hydroxy-benzylidene-acetone is dissolved in the alcohol by heating in a flask fitted with a reflux condenser. The n-propyl-p-toluene-sulphonate is added to the solution followed by the potassium hydroxide dissolved in the minimum of water. The flask is heated under reflux for one and a half hours then cooled and poured into 2½ litres of water. The p-n-propoxy-benzylidene-acetone is thrown out of solution as a light brown oil which crystallises on cooling. The solid is filtered, washed with water and recrystallised from ethyl alcohol to give pale yellow crystals, m.pt. 49° - 50°C. Yield 63%.

	Found:	C, 76.52; H, 7.91%
$C_{13}H_{16}O$ requires:		C, 76.4 ; H, 7.84%

The compound is soluble in alcohol and in acetone but insoluble in water.

1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate

(a) 1-piperidino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride



10.0 gm. (1.0 mol.) p-n-propoxy-benzylidene acetone
2.5 gm. (1.7 mol.) paraformaldehyde
6.5 gm. (1.1 mol.) piperidine hydrochloride
15.0 ml. ethyl alcohol (absolute)

The p-n-propoxy-benzylidene-acetone and the piperidine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and added to the flask at intervals over a period of 30 minutes while refluxing. A clear solution is obtained which crystallises rapidly on cooling to form a mass of light brown crystals. The crystals are filtered, washed with anhydrous ether, and recrystallised from alcohol to give white crystals, m.pt. 195°- 196°C. Yield 43%

The compound is soluble in water and in alcohol but insoluble in ether.

Found: N, 4.3%
$C_{19}H_{27}O_2N$,HCl requires: N, 4.15%

(b) Phenylhydrazone of 1-piperidino-5-(4'-n-propoxy-phenyl)-Δ-penten-3-one hydrochloride

5.0 gm. $C_{19}H_{27}O_2N$,HCl
1.6 gm. phenylhydrazine
1.6 gm. acetic acid (glacial)
20.0 gm. ethyl alcohol (95%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling the phenylhydrazone crystallises. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 145°-146°C. Yield, 83%.

The compound is slightly soluble in cold alcohol, more soluble in warm alcohol. It is insoluble in water.

Found: N, 9.94%
$C_{25}H_{33}ON_3$,HCl requires N, 9.83%

(c) 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate.

$C_3H_7O.C_6H_4.CH{:}C(=N.NH.C_6H_5).CH_2.CH_2.N\,C_5H_{10}HCl$

$\longrightarrow$ $C_3H_7O.C_6H_4.CH(-N(C_6H_5)-N=)CH_2.C.CH_2.CH_2.NC_5H_{10},HCl$

$\longrightarrow$ base $\longrightarrow$ tartrate

2.5 gm. phenylhydrazone
25.0 ml. hydrochloric acid (N/1)

The phenylhydrazone is heated with the hydrochloric acid under reflux on a steam-bath for 20 minutes. The conversion to the pyrazoline takes place rapidly and a greenish coloured solution is produced which deposits an oily layer on cooling. The oily layer crystallises on standing. The pyrazoline hydrochloride is recrystallised from hot water to give white crystals, m.pt. 196°-197°C.

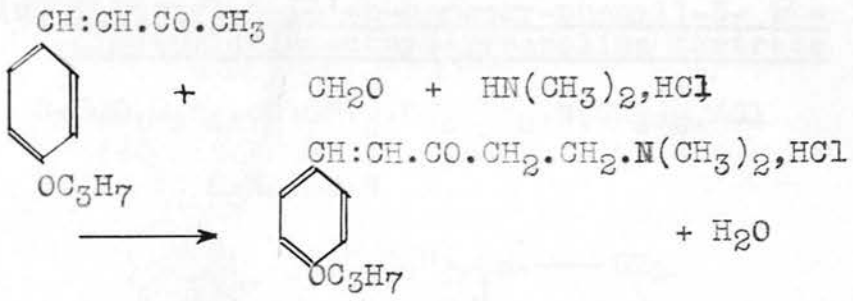
The tartrate is formed by the addition of sodium hydroxide to the solution of the hydrochloride. The free base is liberated and is taken up in ether, the ether solution is washed with water and dried over anhydrous potassium carbonate. The ether is removed on the steam-bath and leaves the base as a yellow coloured viscid liquid. The tartrate is formed by the addition of tartaric acid in alcohol and recrystallised from alcohol-petroleum-ether to give pale yellow crystals, m.pt. 45°-46°C. Yield 43%.

The compound is soluble in water and in alcohol. A small portion placed on the tip of the tongue gives a pronounced local anesthetic action.

Found: N, 7.70%
$C_{25}H_{33}ON_3$,HCl requires N, 7.805%

1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate.

(a) 1-Dimethylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride



10.0 gm. (1.0 mol.) p-n-propoxy-benzylidene acetone.
2.5 gm. (1.7 mol.) paraformaldehyde
4.5 gm. (1.1 mol.) dimethylamine hydrochloride
10.0 ml. ethyl alcohol (absolute)

The p-n-propoxy-benzylidene acetone and the dimethylamine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and added to the flask over a period of 30 minutes while refluxing. A clear solution is obtained which crystallises with some difficulty. Ether (10.0 ml.) is added and on prolonged cooling in the refrigerator crystallisation takes place. The solid is transferred to a filter washed with anhydrous ether and recrystallised from acetone-ether to give white crystals, m.pt. 132°-133°C. Yield 35%.

The compound is soluble in water and in alcohol but insoluble in ether.

Found: N, 4.82%
$C_{16}H_{23}O_2N$,HCl requires: N, 4.70%

(b) Phenylhydrazone of 1-dimethylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

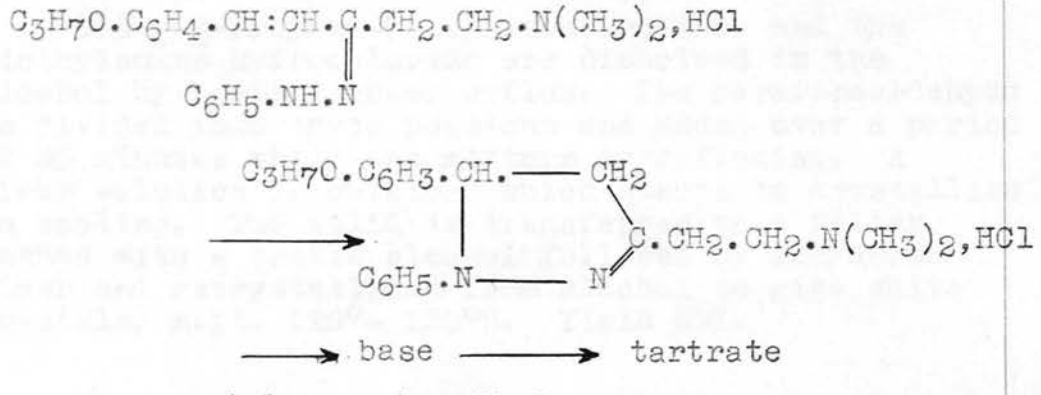
5.0 gm. $C_{16}H_{23}O_2N$,HCl
1.8 gm. phenylhydrazine
1.8 gm. acetic acid (glacial)
10.0 ml. ethyl alcohol

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and acetic acid added. On cooling the phenylhydrazone crystallises out. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 158°-159°C. Yield 65%.

The compound is slightly soluble in cold alcohol and slightly more soluble in warm alcohol. It is insoluble in water.

Found: N, 10.84%
$C_{22}H_{29}O_1N_3$,HCl requires: N, 11.06%

(c) 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate



4.0 gm. phenylhydrazone
40.0 ml. hydrochloric acid N/1

The phenylhydrazone is heated with the hydrochloric acid for thirty minutes in a flask fitted with a reflux condenser. A green coloured solution of the pyrazoline hydrochloride is rapidly formed and on cooling the hydrochloride is deposited as a green viscous liquid which crystallises after standing several hours. The solid is transferred to a filter, washed with the minimum of water and recrystallised from hot water to give white crystals, m.pt.125°-126°C. Yield 54%.

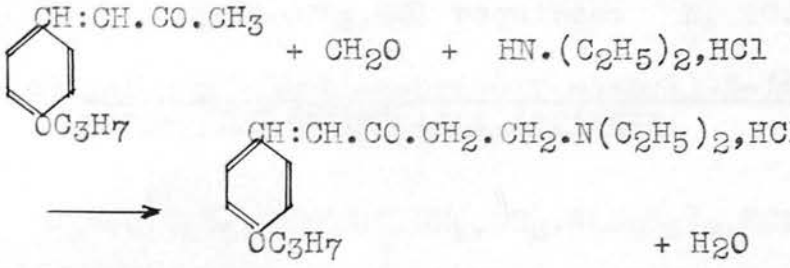
The compound isslightly soluble in cold water and more soluble in alcohol. A small portion placed on the tip of the tongue produces a pronounced local anaesthetic action.

Found: N, 10.66%
$C_{22}H_{29}ON_3$,HCl requires: N, 10.84%

The tartrate is formed by adding the equivalent of tartaric acid in alcohol to the base and recrystallising from acetone to give a yellow powder, m.pt. 56°-57°C.

1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate

(a) 1-diethyl-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride



10.0 gm. (1.0 mol.) p-n-propoxy-benzylidene-acetone
2.5 gm. (1.7 mol.) paraformaldehyde
4.5 gm. (1.1 mol.) diethylamine hydrochloride
10.0 ml. ethyl alcohol (absolute)

The p-n-propoxy-benzylidene acetone and the diethylamine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and added over a period of 30 minutes while the mixture is refluxing. A clear solution is obtained which starts to crystallise on cooling. The solid is transferred to a filter, washed with a little alcohol followed by anhydrous ether and recrystallised from alcohol to give white crystals, m.pt. 129°- 130°C. Yield 52%.

The compound is soluble in water and in alcohol. It is insoluble in ether.

Found: N, 4.32%
$C_{18}H_{27}O_2N$,HCl requires: N, 4.40%

(b) Phenylhydrazone of 1-diethylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

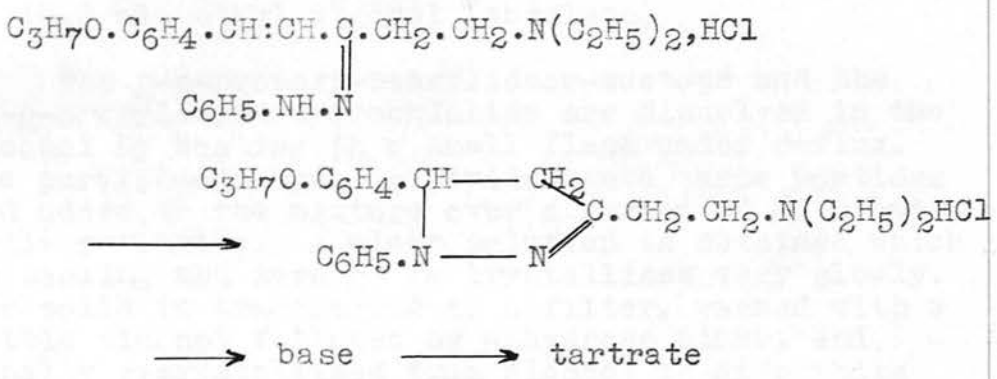
5.0 gm. $C_{18}H_{27}O_2N$,HCl
1.66 gm. phenylhydrazine
1.66 gm. acetic acid (glacial)
10.0 ml. ethyl alcohol (95%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling and scratching the phenylhydrazone crystallises out. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow crystals, m.pt. 155°- 156°C. Yield 63%.

The compound is only very slightly soluble in cold alcohol and more soluble in warm alcohol. It is insoluble in water.

Found: N, 10.31%
$C_{24}H_{33}ON_3$,HCl requires: N, 10.11%

(c) 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-diethyl-amino-ethyl-pyrazoline tartrate.



4.0 gm. phenylhydrazone
40.0 ml. hydrochloric acid (N/1)

The phenylhydrazone is heated under reflux with the hydrochloric acid on a steam-bath for 30 minutes. The conversion to the pyrazoline takes place smoothly and forms a green coloured solution which deposits a viscous liquid on cooling. On standing for several hours crystallisation takes place. The solid is filtered, washed with a little water and recrystallised from hot water to give white crystals, m.pt. 94°-95°C. Yield 48%.

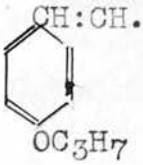
The compound is slightly soluble in cold water, more soluble in alcohol. A small portion placed on the tip of the tongue produced a pronounced local anaesthetic action.

Found: N,10.04%
$C_{24}H_{33}ON_3$,HCl requires: N, 10.11%

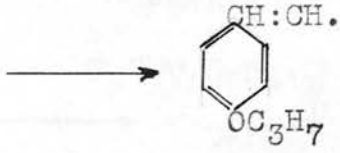
The tartrate is formed by adding the equivalent of tartaric acid to the base and recrystallising from alcohol-petrol-ether to give a pale yellow powder, m.pt. 54°-55°C.

1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate

(a) 1-Di-n-propylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride



+ CH_2O + $HN(C_3H_7)_2$,HCl



+ H_2O

10.0 gm. (1.0 mol.) p-n-propoxy-benzylidene acetone
2.5 gm. (1.7 mol.) paraformaldehyde
7.4 gm. (1.1 mol.) di-n-propylamine hydrochloride
10.0 ml. ethyl alcohol (absolute)

The p-n-propoxy-benzylidene-acetone and the di-n-propylamine hydrochloride are dissolved in the alcohol by heating in a small flask under reflux. The paraformaldehyde is divided into three portions and added to the mixture over a period of 30 minutes while refluxing. A clear solution is obtained which on cooling and scratching crystallises very slowly. The solid is transferred to a filter, washed with a little alcohol followed by anhydrous ether, and finally recrystallised from alcohol to give white crystals, m.pt. 115°- 116°C. Yield 58%.

The compound is slightly soluble in water, more soluble in alcohol but insoluble in ether.

Found : N, 4.13%
$C_{20}H_{31}O_2N$,HCl requires: N, 3.96%

(b) Phenylhydrazone of 1-di-n-propylamino-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

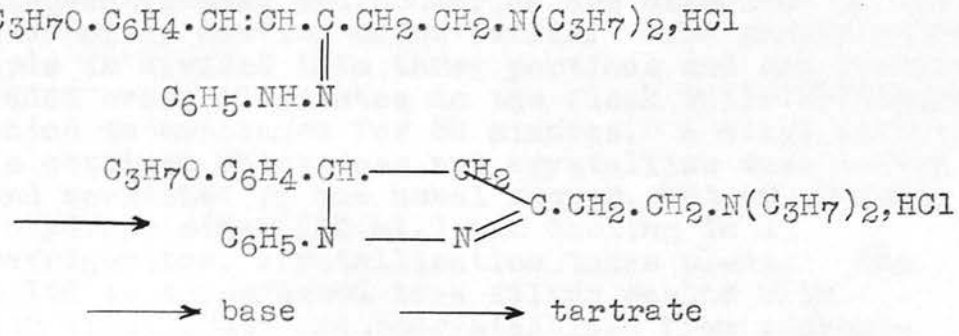
4.0 gm. $C_{20}H_{31}O_2N$.HCl
1.18 gm. phenylhydrazine
1.18 gm. acetic acid (glacial)
10.0 ml. ethyl alcohol (95%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling the phenylhydrazone crystallises out. The crystals are transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 167°- 168°C. Yield 74%.

The compound is only slightly soluble in cold alcohol and not very soluble in warm alcohol. It is insoluble in water

Found: N, 9.32%
$C_{26}H_{37}ON_3$,HCl requires: N, 9.47%

(c) 1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate



3.0 gm. Phenylhydrazone
30.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

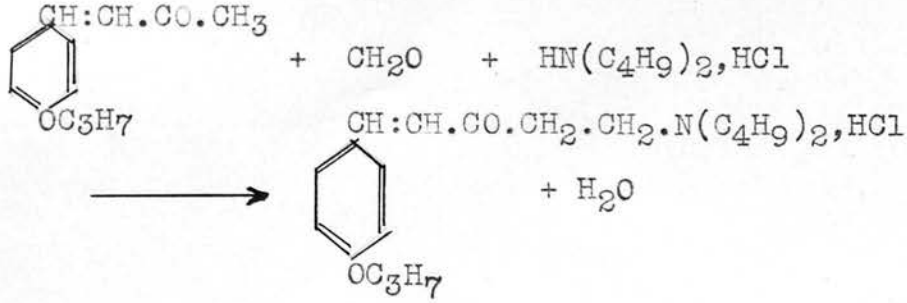
The phenylhydrazone is heated with the hydrochloric acid and the alcohol in a flask fitted with a reflux condenser. The pyrazoline hydrochloride is formed as a green coloured solution and is deposited as a viscous liquid on cooling. The hydrochloride is re-dissolved by adding water (20 ml.) and the base liberated by the addition of sodium hydroxide. The base is taken up in ether, the ether solution washed with water, dried and the ether removed on the steam-bath. The tartrate is formed by adding to the base the equivalent amount of tartaric acid dissolved in alcohol and recrystallising from acetone to give pale yellow crystals, m.pt. 56°-58°C. Yield 47%.

The compound is slightly soluble in water and very soluble in alcohol. A small portion placed on the tip of the tongue produces local anaesthesia.

Found: N, 7.64%
$C_{26}H_{37}ON_3,C_4H_6O_6$ requires: N, 7,54%

1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate

(a) 1-di-n-butylamino-5-(4'-n-propoxy-phenyl)-Δ 4-penten-3-one hydrochloride



7.0 gm. (1.0 mol.) p-n-propoxy-benzylidene acetone
1.75 gm. (1.7 mol.) paraformaldehyde
5.3 gm. (1.1 mol.) di-n-butylamine hydrochloride
10.0 gm. ethyl alcohol (absolute)

The p-n-propoxy-benzylidene acetone and the di-n-butylamine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and one portion added every 10 minutes to the flask while refluxing, which is continued for 30 minutes. A clear solution is obtained which does not crystallise when cooled and scratched in the usual manner, but on adding anhydrous ether (10 ml.) and cooling in a refrigerator, crystallisation takes place. The solid is transferred to a filter washed with anhydrous ether and recrystallised from alcohol-ether to give white crystals, m.pt. 117°-118°C. Yield 42%.

The compound is soluble in water and very soluble in alcohol, but insoluble in ether.

Found: N, 3.72%
$C_{22}H_{35}O_2N$,HCl requires: N, 3.67%

(b) Phenylhydrazone of 1-phenyl-5-(4'-n-propoxy-phenyl)-Δ^4-penten-3-one hydrochloride

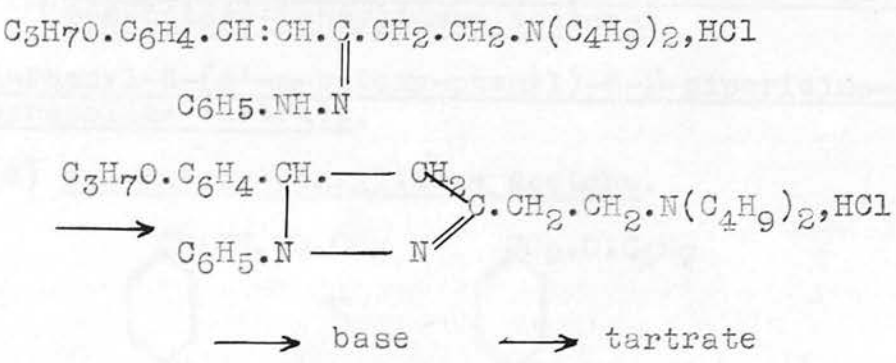
4.0 gm. $C_{22}H_{35}O_2N$,HCl
1.13 gm. phenylhydrazine
1.13 gm. acetic acid (glacial)
10.0 ml. ethyl alcohol (59%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling the phenylhydrazone crystallises out. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 163°-164°C. Yield 68%.

The phenylhydrazone is only slightly soluble in cold alcohol; but more soluble in warm alcohol. It is insoluble in water.

Found: N, 8.88%
$C_{28}H_{37}ON_3$,HCl requires: N, 8.89%

1-Phenyl-5-(4'-n-propoxy-phenyl)-3-β di-n-butylamino-ethyl-pyrazoline tartrate



2.5 gm. phenylhydrazone
25.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

The phenylhydrazone is heated with the alcohol and the hydrochloric acid on a steam-bath under reflux for 40 minutes. The conversion to the pyrazoline is slow and more prolonged heating is necessary to bring about the completion of the reaction. Water (20.0 ml.) is added and the base liberated by the addition of sodium hydroxide solution. The base is extracted with ether; the ether solution washed with water, dried and the ether removed on the steam-bath. The tartrate is formed by the addition of the requisite amount of tartaric acid dissolved in alcohol and the tartrate recrystallised from alcohol-petroleum-ether to give pale yellow crystals, m.pt. 67°-69°C. Yield 38%.

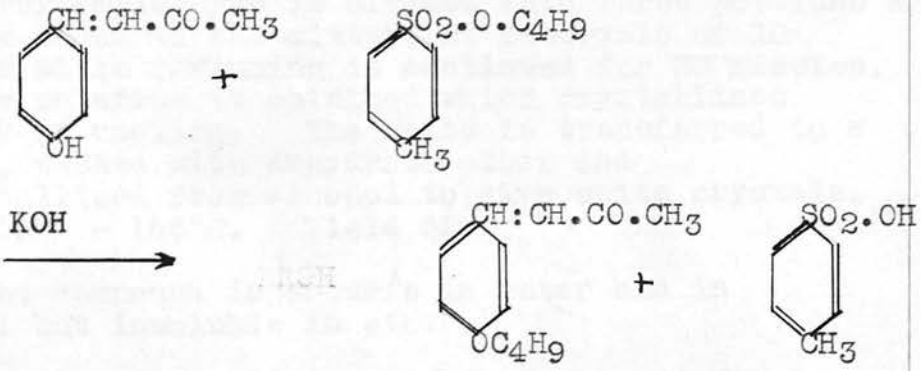
The compound is slightly soluble in water and more soluble in alcohol. A small portion placed on the tip of the tongue gives a slight sensation of local anaesthesia.

Found, N, 7.65%
$C_{28}H_{37}ON_3, C_4H_6O_6$ requires: N, 7.75%

(4) β-Amino-ketones and related pyrazolines derived from p-n-butoxy-benzylidene acetone.

1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate.

(a) p-n-Butoxy-benzylidene acetone.



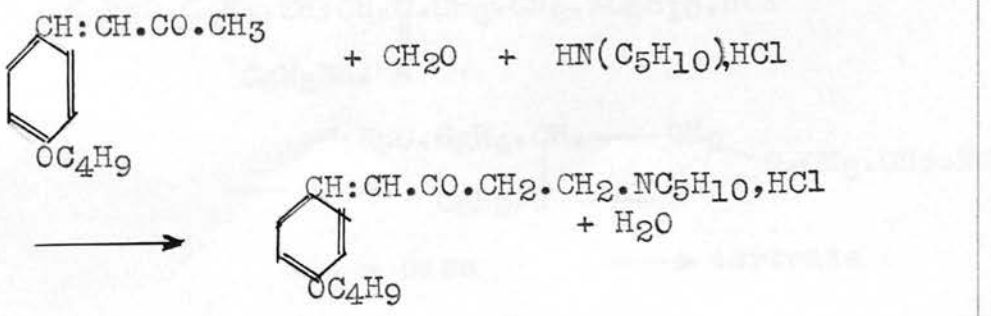
50.0	gm.	p-hydroxy-benzylidene-acetone
71.0	gm.	n-butyl-p-toluene sulphonate.
21.6	gm.	potassium hydroxide
154.0	ml.	ethyl alcohol
1600.0	ml.	water

The p-hydroxy-benzylidene-acetone is dissolved in the alcohol by heating in a flask fitted with a reflux condenser. The n-butyl-p-toluene-sulphonate is added to the solution followed by the potassium hydroxide dissolved in the minimum of water. The flask is heated under reflux for two hours and after cooling the contents are poured into the water. The p-n-butoxy-benzylidene-acetone is thrown out of solution as a yellow oil which crystallises on standing. The solid is transferred to a filter, washed with water, dried and recrystallised from alcohol to give pale yellow crystals, m.pt. 55° - 56°C. Yield 72%.

The compound is soluble in alcohol and acetone but insoluble in water.

Found: C, 77.23%; H, 8.47%
$C_{14}H_{18}O_2$ requires: C, 77.05%; H, 8.26%.

(b) 1-piperidino-5-(4'-n-butoxy-phenyl)-Δ⁴-penten-3-one hydrochloride



8.0 gm. (1.0 mol.) p-n-butoxy-benzylidene acetone.
1.87 gm. (1.7 mol.) paraformaldehyde
4.90 gm. (1.1 mol.) piperidine hydrochloride
20.0 ml. ethyl alcohol (absolute)

The p-n-butoxy-benzylidene acetone and the piperidine hydrochloride are dissolved in the alcohol by heating under reflux on the steam-bath. The paraformaldehyde is divided into three portions and a third added to the mixture at intervals of 10 minutes while refluxing is continued for 30 minutes. A clear solution is obtained which crystallises rapidly on cooling. The solid is transferred to a filter, washed with anhydrous ether and recrystallised from alcohol to give white crystals, m.pt. 185° - 186°C. Yield 62%.

The compound is soluble in water and in alcohol but insoluble in ether.

Found: N, 4.02%
$C_{20}H_{29}O_2N,HCl$ requires: N, 3.98%.

(c) Phenylhydrazone of 1-piperidino-5-(4'-n-butoxy-phenyl)-Δ^4-3-one hydrochloride.

5.0 gm. $C_{20}H_{29}O_2N,HCl$
1.54 gm. phenylhydrazine
1.54 gm. acetic acid (glacial)
20.0 ml. ethyl alcohol (95%).

The ketone is dissolved in the ethyl alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling the phenylhydrazone crystallises out. The solid is transferred to a filter, washed with a little alcohol and recrystallised from alcohol to give yellow needles, m.pt. 128° - 129°C. Yield 76%.

The compound is slightly soluble in cold alcohol, more soluble in warm alcohol but insoluble in water.

Found: N, 9.46%
$C_{26}H_{35}ON_3,HCl$ requires: N, 9.51%.

(d) 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-piperidino-ethyl-pyrazoline tartrate.

$C_4H_9O.C_6H_4.CH:CH.C(=N.NH.C_6H_5).CH_2.CH_2.NC_5H_{10},HCl$

$\longrightarrow$ $C_4H_9O.C_6H_4.CH(-N(C_6H_5)-N=C<)-CH_2-C.CH_2.CH_2.NC_5H_{10},HCl$

$\longrightarrow$ base $\longrightarrow$ tartrate

2.5 gm. phenylhydrazone
25.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

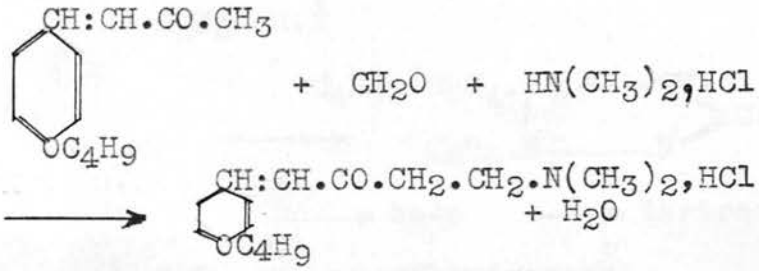
The phenylhydrazone is heated for 30 minutes with the hydrochloric acid and the alcohol. The conversion to the pyrazoline takes place smoothly and rapidly giving a green coloured solution. Water (20 ml.) is added and the solution made slightly alkaline with sodium hydroxide solution. The free base is liberated and is taken up in ether. The ether solution is washed with water, dried over anhydrous potassium carbonate and the ether removed on the steam-bath. The tartrate is formed by adding to the base the requisite amount of tartaric acid dissolved in alcohol. Recrystallised from acetone it forms yellow crystals, m.pt. 58° - 59°C. Yield 54%.

The compound is soluble in water and in alcohol. A small portion placed on the tip of the tongue gives a pronounced local anaesthetic action.

Found: N, 7.64%
$C_{26}H_{35}ON_3, C_4H_6O_6$ requires: N, 7.59%.

1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-dimethylamino-ethyl pyrazoline tartrate.

(a) 1-Dimethylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



8.0 gm. (1.0 mol.) p-n-butoxy-benzylidene-acetone
1.87 gm. (1.1 mol.) paraformaldehyde.
3.30 gm. (1.1 mol.) dimethylamine hydrochloride
10.0 ml. ethyl alcohol (absolute).

The p-n-butoxy-benzylidene acetone and the dimethylamine are dissolved in the alcohol by heating under reflux on the steam-bath. The paraformaldehyde is divided into three portions and added at 10 minute intervals. A clear solution is obtained which does not crystallise on standing, but on adding 10 ml. anhydrous ether and cooling in a refrigerator crystallisation takes place. The solid is transferred to a filter, washed with anhydrous ether and recrystallised from alcohol to give white crystals, m.pt. 128° - 129°C. Yield 56%.

The compound is soluble in water and in alcohol but insoluble in ether.

	Found:	N, 5.01%
$C_{17}H_{25}O_2N,HCl$	requires:	N, 4.49%.

(b) Phenylhydrazone of 1-dimethylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

5.0 gm.	$C_{17}H_{25}O_2N,HCl$
1.73 gm.	phenylhydrazine
1.73 gm.	acetic acid (glacial)
20.0 ml.	ethyl alcohol (95%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. On cooling the phenylhydrazone crystallises out. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to form yellow needles, m.pt. 138° - 139°C. Yield 76%.

The compound is slightly soluble in cold alcohol, more soluble in warm alcohol. It is insoluble in water.

	Found:	N, 10.62%
$C_{23}H_{31}ON_3,HCl$	requires:	N, 10.46%.

(c) 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-dimethylamino-ethyl-pyrazoline tartrate.

$$C_4H_9O.C_6H_4.CH{:}CH.C(=N.NH.C_6H_5)\,CH_2.CH_2.N(CH_3)_2,HCl$$

$$\longrightarrow\ C_4H_9O.C_6H_4.CH(N(C_6H_5).N=)\,CH_2\,C.CH_2.CH_2.N(CH_3)_2,HCl$$

$$\longrightarrow \text{base} \longrightarrow \text{tartrate}$$

2.5 gm.	phenylhydrazone
25.0 ml.	hydrochloric acid (N/1)
10.0 ml.	ethyl alcohol.

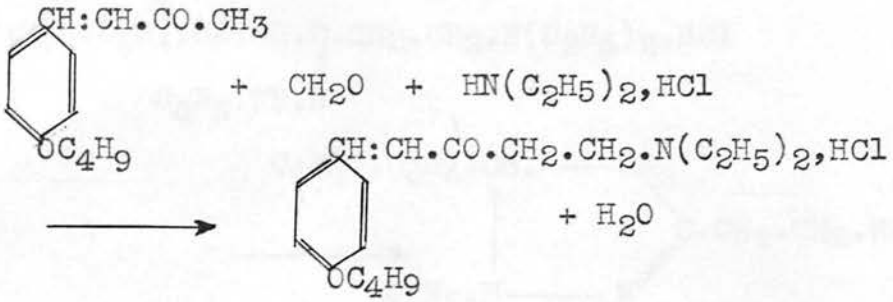
The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol for 30 minutes. The conversion to the pyrazoline takes place smoothly and a greenish coloured solution is produced. Water (20 mol.) is added and the base is liberated by the addition of sodium hydroxide solution. The base is taken up in ether, washed with water and dried over anhydrous potassium carbonate. The tartrate is formed by the addition of the equivalent amount of tartaric acid in alcohol to the dried base. Recrystallised from acetone it forms pale yellow crystals, m.pt. 63° - 65°C. Yield 54%.

The compound is soluble in water and in alcohol, but insoluble in ether. A small portion on the tip of the tongue produces a pronounced local anaesthetic action.

Found: N, 8.34%
$C_{23}H_{31}O_4N_3, C_4H_6O_6$ requires: N, 8.15%.

1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-di-ethylamino-ethyl-pyrazoline tartrate.

(a) 1-Diethylamino-5-(4'-p-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



8.0 gm. (1.0 mol.) p-n-butoxy-benzylidene-acetone
1.87 gm. (1.7 mol.) paraformaldehyde
4.45 gm. (1.1 mol.) diethylamine hydrochloride
10.0 ml. ethyl alcohol (absolute).

The p-n-butoxy-benzylidene-acetone and the diethylamine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and a third added to the mixture at intervals of 10 minutes while refluxing. A clear solution is obtained from which crystals separate on cooling. The solid is transferred to a filter, washed with anhydrous ether and recrystallised from alcohol to give white crystals, m.pt. 131° - 132°C. Yield 58%.

The compound is soluble in water and in alcohol but insoluble in ether.

Found: N, 4.24%
$C_{19}H_{29}O_2N, HCl$ requires: N, 4.12%.

(b) Phenylhydrazone of 1-diethylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

5.0 gm. $C_{19}H_{29}O_2N, HCl$
1.62 gm. phenylhydrazine
1.62 gm. acetic acid (glacial)
15.0 ml. ethyl alcohol (95%).

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. The phenylhydrazone crystallises/

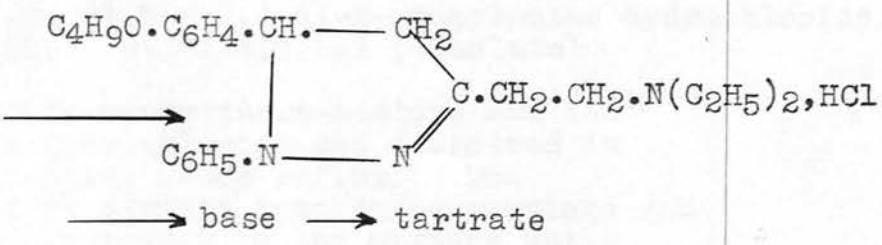
crystallises readily on cooling. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 145° - 146°C. Yield 78%.

The compound is soluble in alcohol but insoluble in water.

Found: N, 9.84%
$C_{25}H_{35}ON_3$,HCl requires: N, 9.78%.

(c) 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-diethylamino-ethyl-pyrazoline tartrate.

$C_4H_9O.C_6H_4.CH:CH.C(=N.NH.C_6H_5).CH_2.CH_2.N(C_2H_5)_2$,HCl



→ base → tartrate

2.5 gm. phenylhydrazone
25.0 gm. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol on a steam-bath for 30 minutes. The conversion to the pyrazoline takes place smoothly and a clear solution is produced. After cooling, water (20 ml.) is added and the solution made slightly alkaline with sodium hydroxide. The base which is thrown out of solution is taken up in ether. The etherial solution is dried and the ether removed on the steam-bath. The tartrate is formed by the addition to the base of the equivalent amount of tartaric acid in alcohol. Recrystallised from acetone it forms pale yellow crystals, m.pt. 56° - 57°C. Yield 43%.

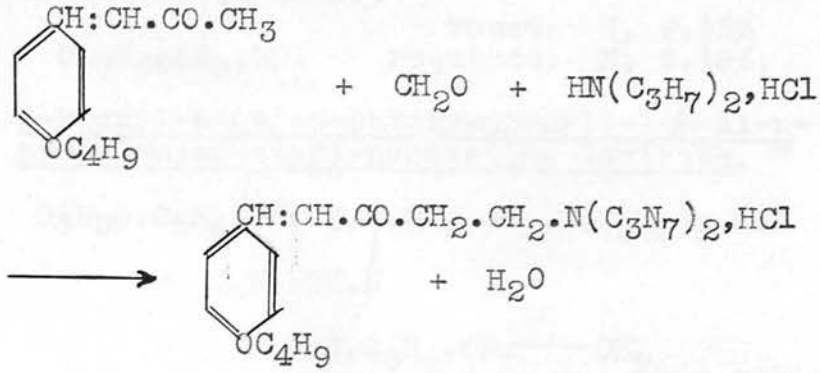
The compound is soluble in water and in alcohol. A small portion placed on the tip of the tongue gives a pronounced local anaesthetic action.

Found: N, 7.68%
$C_{25}H_{35}ON_3,C_4H_6O_6$ requires: N, 7.33%.

1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate.

(a)/

(a) 1-Di-n-propylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



8.0 gm. (1.0 mol.) p-n-butoxy-benzylidene-acetone.
1.87 gm. (1.7 mol.) paraformaldehyde
5.55 gm. (1.1 mol.) di-n-propylamine hydrochloride.
15.0 ml. ethyl alcohol (absolute)

The p-n-butoxy-benzylidene-acetone and the di-n-propylamine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and a third added at intervals to the mixture while refluxing for 30 minutes. A clear solution is obtained which does not crystallise in the usual manner on cooling. Anhydrous ether (10 ml.) is added and on cooling in the refrigerator crystallisation takes place. The solid is transferred to a filter, washed with ether and recrystallised from alcohol to give white crystals, m.pt. 112° - 113°C. Yield 62%.

The compound is slightly soluble in water and soluble in alcohol but insoluble in ether.

	Found:	N, 3.93%
$C_{21}H_{33}O_2N$, HCl	requires:	N, 3.81%.

(b) Phenylhydrazone of 1-di-n-propylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

5.0 gm. $C_{21}H_{33}O_2N$,HCl
1.46 gm. phenylhydrazine
1.46 gm. acetic acid (glacial)
10.0 ml. ethyl alcohol (90%).

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. Crystallisation takes place readily on cooling. The solid is transferred to a filter, washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 150° - 151°C. Yield 84%.

The/

The compound is slightly soluble in alcohol but insoluble in water.

Found: N, 9.35%
$C_{27}H_{39}ON_3,HCl$ requires: N, 9.18%.

(c) 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-di-n-propylamino-ethyl-pyrazoline tartrate.

$$C_4H_9O.C_6H_4.CH{:}CH.\underset{\underset{C_6H_5.NH.N}{\|}}{C}.CH_2.CH_2.N(C_3H_7)_2,HCl$$

$$\longrightarrow \quad C_4H_9O.C_6H_4.CH\begin{cases}-CH_2-C.CH_2.CH_2.N(C_3H_7)_2,HCl \\ C_6H_5.N-N\end{cases}$$

$\longrightarrow$ base $\longrightarrow$ tartrate

3.0 gm. phenylhydrazone
30.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

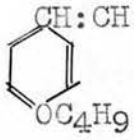
The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol for 30 minutes. Conversion to the phenylhydrazone takes place smoothly. The solution is cooled and water (20 ml.) is added and the solution made slightly alkaline with sodium hydroxide. The free base is liberated and is taken up in ether. The ether solution is washed, dried, and the ether removed on the steam-bath. The tartrate is formed by the addition to the base of the equivalent amount of tartaric acid dissolved in alcohol. Recrystallised from acetone it forms pale yellow crystals, m.pt. 60° - 61°C. Yield 48%.

The compound is soluble in water and in alcohol but insoluble in ether. A small portion placed on the tip of the tongue produces a local anaesthetic action.

Found: N, 7.47%
$C_{27}H_{39}ON_3,C_4H_6O_6$ requires: N, 7.355%.

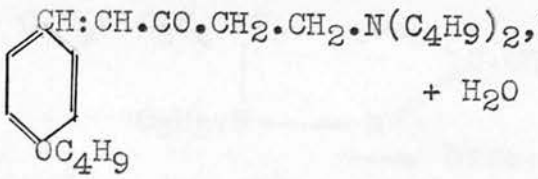
1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate.

(a) 1-Di-n-butylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



$+ \quad CH_2O \quad + \quad HN(C_4H_9)_2,HCl$

$\longrightarrow$



8.0 gm. (1.0 mol.) p-n-butoxy-benzylidene-acetone
1.87 gm. (1.7 mol.) paraformaldehyde
6.5 gm. (1.1 mol.) di-n-butylamine hydrochloride
15.0 ml. ethyl alcohol (absolute).

The p-n-butoxy-benzylidene acetone and the di-n-butylamine hydrochloride are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and a third added at intervals of 10 minutes to the mixture while refluxing. The heating is carried on for 30 minutes. A clear solution is obtained which does not crystallise on standing, but on adding ether (10 mol.) crystallisation takes place. Recrystallisation from alcohol gives white crystals, m.pt. 111° - 112°C. Yield 44%.

The compound is slightly soluble in water and soluble in alcohol.

Found: N, 3.34%.
$C_{23}H_{37}O_2N,HCl$ requires: N, 3.54%.

(b) Phenylhydrazone of 1-di-n-butylamino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

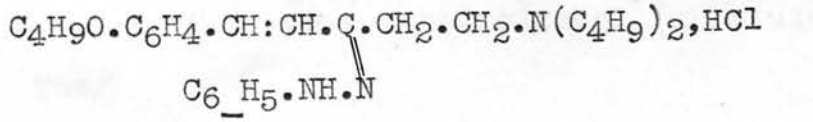
5.0 gm. $C_{23}H_{37}O_2N,HCl$
1.37 gm. phenylhydrazine
1.37 gm. acetic acid (glacial)
15.0 ml. ethyl alcohol (95%)

The unsaturated ketone is dissolved in the alcohol by heating and the phenylhydrazine and the acetic acid added. The phenylhydrazone crystallises rapidly and is recrystallised from alcohol to give yellow needles, m.pt. 133° - 134°C. Yield 76%.

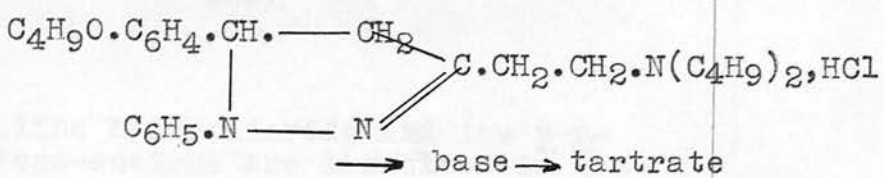
The compound is slightly soluble in alcohol.

Found: N, 8.54%
$C_{29}H_{43}ON_3,HCl$ requires: N, 8.65%.

(c) 1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-di-n-butylamino-ethyl-pyrazoline tartrate.



→



3.0 gm. phenylhydrazone
30.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol.

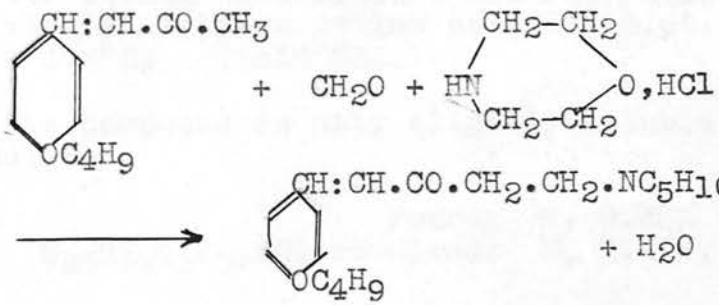
The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol. The conversion to the pyrazoline is slow and requires refluxing for 40 minutes before a clear solution is obtained. The base is liberated with sodium hydroxide and taken up in ether. The ether solution is washed with water, dried and the ether removed on the steam-bath. The tartrate is formed by the addition to the base of the equivalent amount of tartaric acid in alcohol, and finally recrystallised from acetone to give pale yellow crystals, m.pt. 63° - 64°C. Yield 35%.

The compound is soluble in water and in alcohol. A small portion placed on the tip of the tongue produces a slight local anaesthetic action.

Found: N, 6.85%
$C_{29}H_{43}O_8N_3,C_4H_6O_6$ requires: N, 7.01%.

1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-morpholino-ethyl-pyrazoline tartrate.

(a) 1-Morpholino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.



4.0 gm. (1.0 mol.) p-n-butoxy-benzylidene-acetone
0.93 gm. (1.7 mol.) paraformaldehyde
2.26 gm.(1.1 mol.) morpholine hydrochloride
6.0 ml. ethyl alcohol (absolute).

The/

The morpholine hydrochloride and the p-n-butoxy-benzylidene-acetone are dissolved in the alcohol by heating under reflux. The paraformaldehyde is divided into three portions and a third added at intervals to the mixture while refluxing for 30 minutes. A clear solution is obtained which rapidly crystallises on cooling. The crystals are transferred to a filter, washed with alcohol and recrystallised from alcohol to give white crystals, m.pt. 170° - 171°C. Yield 68%.

The compound is slightly soluble in water and slightly soluble in alcohol.

	Found:	N, 3.84%
$C_{19}H_{27}O_3N,HCl$	requires:	N, 3.96%.

(b) Phenylhydrazone of 1-morpholino-5-(4'-n-butoxy-phenyl)-Δ^4-penten-3-one hydrochloride.

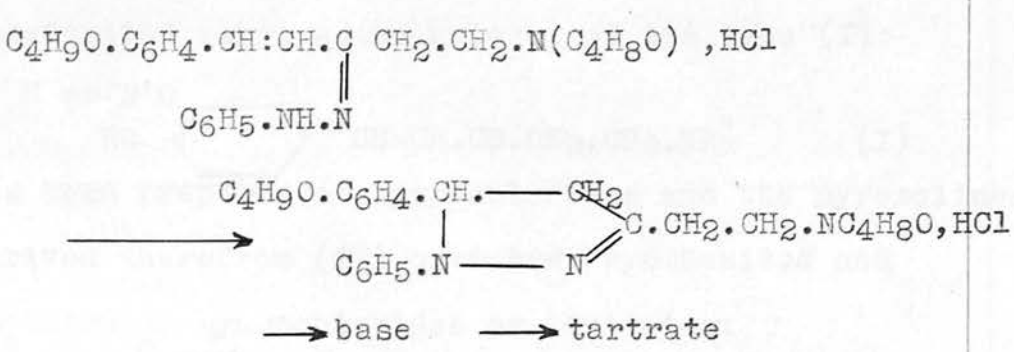
3.0 gm.	$C_{19}H_{27}O_3N,HCl$
0.92 gm.	phenylhydrazine
0.92 gm.	acetic acid (glacial)
10.0 ml.	ethyl alcohol (95%).

The ketone is dissolved in the alcohol by heating and the phenylhydrazine and acetic acid added. On cooling the phenylhydrazone crystallises out. The solid is transferred to a filter washed with alcohol and recrystallised from alcohol to give yellow needles, m.pt. 177° - 178°C. Yield 85%.

The compound is only slightly soluble in alcohol.

	Found:	N, 9.38%
$C_{25}H_{34}O_2N_3,HCl$	requires:	N, 9.45%.

(c) <u>1-Phenyl-5-(4'-n-butoxy-phenyl)-3-β-morpholino-ethyl-pyrazoline tartrate</u>



3.0 gm. phenylhydrazine
30.0 ml. hydrochloric acid (N/1)
10.0 ml. ethyl alcohol

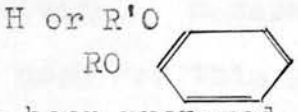
The phenylhydrazone is heated under reflux with the hydrochloric acid and the alcohol for 30 minutes. Conversion to the pyrazoline takes place readily. On cooling the solution, the hydrochloride is thrown out as a green coloured oil which crystallises on standing. The base is liberated with alkali, taken up in ether, the solution washed with water and dried. The ether is removed on the steam-bath and to the base is added an equivalent amount of tartaric acid dissolved in alcohol. The tartrate is recrystallised from acetone to give pale yellow crystals, m.pt. 70°- 72°C. Yield 52%.

The compound is soluble in water and in alcohol. A small portion placed on the tip of the tongue produces a slight anaesthetic action.

Found: N, 7.38%
$C_{25}H_{34}ON_3,C_4H_6O_6$ requires: N, 7.5%

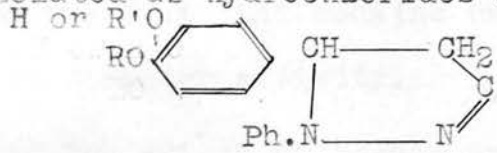
SUMMARY AND CONCLUSIONS

(1) From p-alkoxy and m-p-dialkoxy benzylidene acetones, utilising the Mannich reaction, a series of unsaturated alkyl amino ketones of the type (I):-



(I)

has been prepared as hydrochlorides and the pyrazolines derived therefrom (II) have been synthesised and isolated as hydrochlorides or tartrates:

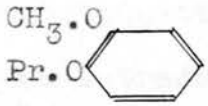
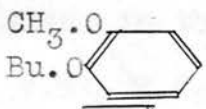
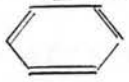


(II)

(2) The new pyrazolines have been found to be potent local anaesthetics for topical and intradermal use.

(3) In examining the topical activities on the cornea of guinea-pigs it was found that the effect of the size of the amino substituents on the β-carbon atom of the 3-ethyl group (i.e. the group NR") varied as shown in the table below:-

TABLE NO. 15

Group in position 5	Amino substituents in order of activity
	$N.Et_2 > N.Me_2 > N.C_5H_{10} > N.Pr_2 > N.Bu_2 > N.(CH_2)_4O.$
	$N.Et_2 > N.Me_2 > N.C_5H_{10} > N.Pr_2 > N.Bu_2 > N(CH_2)_4O.$
	$N.Et_2 > N.Me_2 > N.C_5H_{10} > N.Pr_2 > N.Bu_2 > N.(CH_2)_4O$
	$N.Et_2 > N.Me_2 > N.C_5H_{10} > N.Pr_2 > N.Bu_2 > N.(CH_2)_4O$

The regression lines of the logarithms of the concentration against duration of topical anaesthesia have /

have been found to be parallel in the case of all the pyrazolines and nupercaine. This last drug was therefore chosen as a suitable reference standard of activity. Cocaine, it was found however, could not be used for this purpose on account of the fact that the slope of the regression line in this case differ-:ed from that of the other drugs. This may be due to the fact that cocaine has a pronounced vaso-:constrictor activity.

(4) The effect of change in size of the alkoxy groups substituted in the 5-phenyl nucleus on the topical activity has not been so fully examined, but it appears that the p-n-propoxy derivatives are the most active as indicated in the series:-

p-n-propoxy > p-n-butoxy > m-methoxy-p-n-propoxy > m-methoxy-p-n-butoxy

where the basic amino substituent on the β-carbon of the 3-ethyl group is diethylamino.

(5) The effect of changes in the size of the amino substituents of the β-carbon in the 3-ethyl group on the intradermal activity of the drugs synthesised is given in the following order of activity:-

$N.Et_2 > N.C_5H_{10} > N.Me_2 > N.Pr_2 > N.Bu_2 > N.(CH_2)_4O$.

The effect of changes in the alkoxy groups substituted in the 5-phenyl nucleus follows the series:-

p-n-propoxy > m-methoxy-p-n-propoxy > p-n-butoxy > m-methoxy-p-n-butoxy

where the amino substituent is diethylamino in each case.

(6) The effect of the alkoxy substituents (R.O. and R'.O) upon the toxicity indicates that there is a slight decrease in toxicity with increase in size and number of alkoxy substituents as indicated in the series:-

<u>n</u>-propoxy < <u>n</u>-butoxy < methoxy-<u>n</u>-propoxy < methoxy-<u>n</u>-butoxy

where the basic amino group in the β-carbon of the 3-ethyl substituent is piperidino.

(7) The effect of the amino substituents (N.R") upon toxicity has not been fully examined but the diethylamino compound is more toxic than the piperidino compound where the substituent in the 5-position is <u>3</u>-methoxy-<u>4</u>-<u>n</u>-propoxy-phenyl.

ACKNOWLEDGEMENTS

The author desires to thank Principal H.B. Nisbet for his advice throughout the entire course of this work and for his constant interest in its progress.

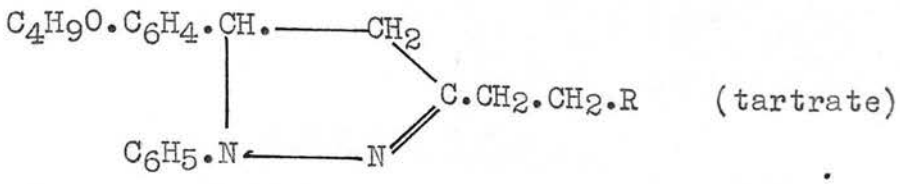
Professor J.H. Gaddum's hospitality and advice are gratefully acknowledged as also the advice and assistance of Dr.T.B.B. Crawford.

The author also desires to thank Mr. A.T. Macdonald of the Heriot-Watt College for carrying out the micro analyses.

A grant from the Carnegie Trust for the Universities in Scotland towards the cost of the animals used in the research is also gratefully acknowledged.

TABLE No.14.

Summary of the pharmacological tests.



4'-n-Butoxy substituted in the phenyl group attached to the position 5 of the pyrazoline molecule.

	Guinea Pig Wheal		Guinea Pig Cornea		Toxicity
	Ratio to Procaine	Therapeutic Value	Ratio to Nupercaine	Therapeutic Value	L.D.50(Mice) mg./kg.
R = Dimethylamino	4.0		0.3		
R = Diethylamino	6.0	3.2	0.4	1.3	(120)
R=Di-n-propylamino	3.0		0.1		
R=Di-n-butylamino	2.0		0.08		
R=Piperidino	4.5	3.3	0.23	1.0	165
Procaine Hyd.	1.0				225
Nupercaine Hyd.			1.0		35
Cocaine Hyd.					110